STEREOSELECTIVE SYNTHESIS OF 1,2-DISUBSTITUED BETA-AMINO ALCOHOLS AND AMINO THIOLS

BY

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DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2020

Urbana, Illinois

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Abstract

This thesis covers the development and implementation of two distinct methodologies, both of which provide access to enantiomerically enriched, vicinally functionalized products. Chapter 1 provides background and a brief introduction of the activation of Group 16 Lewis acids by Lewis bases. Chapter 2 details a method for the catalytic, enantioselective, intermolecular, 1,2-sulfenoamination of alkenes. Functionalization is achieved through the intermediacy of an enantioenriched, configurationally stable thiiranium ion generated by Lewis base activation of a readily available sulfur electrophile. An expedited reaction optimization was achieved by employing multivariate Design of Experiment optimization ultimately resulting for a diverse set of anilines and benzylamines react with different styrenes to afford products in good yield and stereoselectivity. Downstream manipulation of the products is facilitated by deprotonation of the amines to enable carbon-sulfur bond cleavage.

Chapter 3 of this thesis covers the identification of a method amenable to the rapid construction of diverse libraries of 1,2-amino alcohols. A number of methods are examined prior to the identification of 1,2-conjugate addition of aryl and alkyl lithium reagents to Ellman sulfonimines. The use of lithium reagents is key to overcome modest diastereoselectivity and poor reaction rates. A brief scope is explored and stereochemical models are discussed.

Acknowledgement

Every thesis I have read, I find myself stopping to see who helped the author along the way. Without fail the acknowledgments show that a Ph.D is completed with the help and support of a large compliment of people. This dissertation is no exception. First, I would like to thank my family – Jan, Steve and Adam – your constant support during the past six years has not gone unnoticed. This would not have been possible without you and I know that I can always count on you to be there.

In addition to a supportive family, I have been fortunate to find a group of friends at Illinois that quickly became like family. For that I am particularly indebted to Siraj Ali, Dr. Chris Bemis, Connor Delany, Dan Holycross, Bryan Reynolds, and Dr. Andrew Zahrt. Thank you for making this experience simply unforgettable. The antics outside of lab are cherished memories I will carry with me for the rest of my life.

With that said, No Ph.D in organic chemistry is complete without spending a significant amount of time in the laboratory where I have had the fortune to work with some incredible chemists. To Dr. Scott Barazza, Prof. Kevin Robb, Prof. Zhonglin Tao and Prof. Andy Thomas, thank you for your constant mentorship. Your experience, knowledge and willingness to advise an over enthusiastic, young chemist is remarkable. It is safe to say that without all of you I would most certainly be in law school right now. I have also had the fortune to share lab space with some truly unique individuals, exceptional in their own regard. Dr. Soumitra Athavle, Aragorn Laverny, Travis Menard: thank you for making every day a new adventure.

Looking back, I have to thank Prof. Mark Kurth for getting this journey started. When I recall sitting in my college apartment and sending a blind email asking for a research position, I had no idea where it would take me. Thank you for giving me a chance and the guidance to find my own way.

Finally, thank you to Matthew Boudreau, Lindsay Chatkewitz and all of Cancer Journal Club for instilling what I can only imagine will be a lifelong passion for cancer biology and the important problems still left to solve.

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Chapter 1. A Brief Overview of Lewis Base Catalysis[1]

Introduction

In 1923 Brønsted and Lowry concurrently recognized and defined an acid as a species that donates a proton and a base as one that can accept a proton.[2] In the same year, Gilbert N. Lewis proposed a distinct, all encompasing theory that fundamentally changed the way chemists envisioned molecular interactions. Lewis states that "the basic substance furnishes a pair of electrons for a chemical bond" and, the corollary, "the acid substance accepts such a pair".[3] Such a simple statement neatly captured fundamental bond forming processes and quickly became a unifying principle of organic chemistry.

The donation of a lone pair of electrons from a Lewis base to a Lewis acid generally provides the necessary condition to satisfy the Octet rule. This process results in the formation of a stabilized complex. For example, subjecting the highly reactive and toxic Lewis acid boron trifluoride to diethyl ether forms a stable Lewis acid-Lewis base adduct that can readily be manipulated. However, the formation of a more stable complex does not render this adduct unreactive. The resulting $BF_3.\cdot Et_2O$ adduct has been successfully employed in a number of Lewis acid mediated transformations.

In the intervening years, the reactivity of these complexes has been utilized to develop new reactivity and forge new chemical bonds. Classic examples include the Mukaiyama aldol reaction and Sakurai reaction.[4,5] Both transformations rely on the precoordination of a Lewis acid to a carbonyl-containing reactant which provides a complex with enhanced *electrophilicity*. Rationalizing this observation is relatively intuitive - electron density is redistributed toward the Lewis acid rendering the carbonyl carbon more electrophilic and susceptible to nucleophilic attack. Indeed, the rate enhancement brought about by this bond polarization has enabled the development catalytic, enantioselective variants of these transformations.

It would therefore follow that if Lewis acids enhance the *electrophilicity,* Lewis bases should enhance the *nucleophilicity* of a reaction partner. Though not as commonly employed, this is indeed the case. Classic examples include the Morita-Baylis-Hillman reaction and the Hajos-Parrish cyclization in which an enolate or enamine, respectively, are generated possessing

enhanced nucleophilicity (Figure 1).[6,7] Additionally, this type of Lewis base catalysis has been described in Type I aldolases.[8]

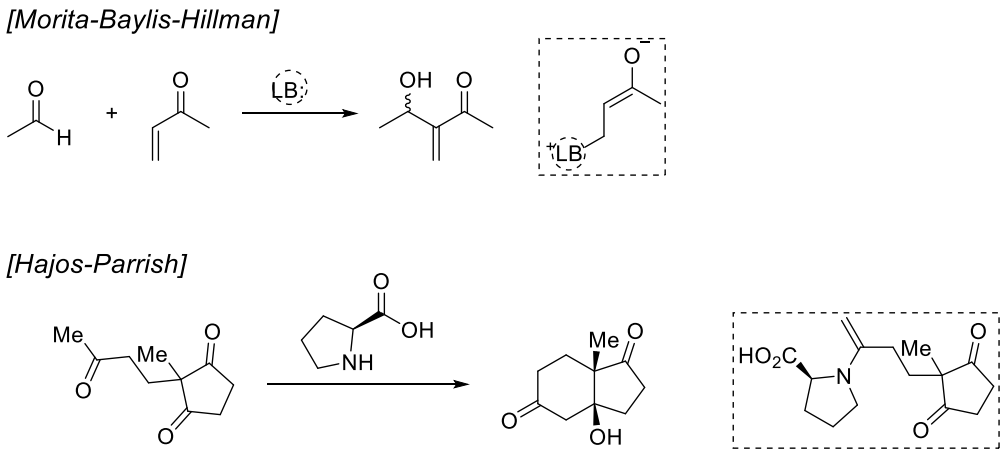


Figure 1. Reactions with increased nucleophilicity from (n→π*) Lewis base catalysis.

However, it should not escape the attention of any modern organic chemist that Lewis bases are readily employed catalytically to enhance the *electrophilicity* of key intermediates. An immediately recognizable species is the acyl-DMAP intermediate (Figure 2). Prior to the 1969 disclosure of DMAP by Steglich and Höfle, acylations of tertiary alcohols by acetic anhydride were considered impossible, even under the action of solvent quantities pyridine; however, employing catalytic amounts of DMAP effected the same transformation in 14 h in 86% yield.[9,10] This dramatic enhancement of reactivity was achieved by forming a highly electrophilic, cationic intermediate which is intercepted by a nucleophile and the catalyst is regenerated.

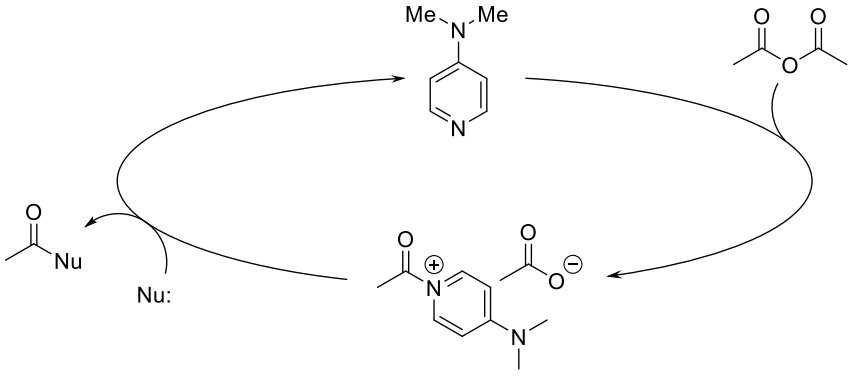


Figure 2. Increased electrophilicity from (n→π*) Lewis base catalysis.

Having introduced two modes in which a Lewis base can serve as a catalyst, it is important to draw distinction between two commonly conflated terms - Lewis base catalysis and nucleophilic catalysis.[11] Although the Lewis base reacts as a nucleophile, it is serving to enhance either the nucleophilic or electrophilic character of a reactive intermediate. By describing the overall process as nucleophilic catalysis there is an implication that only nucleophilic character will be enhanced, which is not the case. Therefore, it is prudent to reserve the terms "nucleophilic" and "electrophilic" for the reactivity patterns observed in individual species and not the mode of catalysis as a whole.

Additionally, a distinction should be drawn between Lewis base catalysis and "ligand-accelerated catalysis". Ligand-Accelerated catalysis describes the phenomenon that the addition of a Lewis-basic ligand gives rise to a more reactive *catalyst*. For example, in titanium-catalyzed epoxidations, titanium is inherently capable of acting as a catalyst without coordination to the Lewis-basic ligand. Coordination of the ligand simply gives rise to a more reactive catalyst. In Lewis base catalysis, the process is not catalytic without the presence of a Lewis base. Upon coordination of the Lewis base, a catalytically competent species is generated which has increased nucleophilic or electrophilic characteristics. This is a subtle, yet important, difference that sets these two modes of catalysis apart.

Thus far, all examples of Lewis base catalysis described can be categorized as an $n \rightarrow \pi^*$ interaction employing the nomenclature developed by Jensen.[12] This interaction occurs when the nonbonding lone pair of the Lewis basic donor interacts with the π^* acceptor orbital. In total there are nine types of donor-acceptor interactions that can occur between filled σ, π, or n type orbitals and unoccupied σ^*, π^*, or n* type orbitals. While $n \rightarrow \pi^*$ interactions are the most widely encountered donor-acceptor type interactions, $n \rightarrow \sigma^*$ type interactions can also promote catalysis.

The consequences of $n \rightarrow \sigma^*$ interactions, specifically the reorganization of electron density in a donor-acceptor complex, were enumerated by Gutmann in a series of empirical rules.[13,14] With respect to the fourth rule concerning charge density variation, Jensen states:

> "*although a donor-acceptor interaction will result in a net transfer of electron density from the donor species to the acceptor species, it will, in the case of polyatomic*

> *species, actually lead to a net increase or "pileup" of electron density at the donor atom of the donor species and to a net decrease or "spillover" of electron density at the acceptor atom of the acceptor species. This results from the accompanying changes in the intramolecular charge distribution induced by the primary donor-acceptor interaction. These disperse the net change in electron density among all the atoms and in so doing, overcompensate for the initial changes induced at the donor and acceptor atoms. This result is important as it contradicts the usual assumption of the organic chemist that the net changes in formal charges remain localized on the donor and acceptor atoms.*"[15]

The following discussion will center on this electron redistribution and how it manifests in n→σ* type interactions. First, three examples – crystallographic, computational and an orbital analysis – will be provided to clarify the electronic effects of donor-acceptor complex formation. Then a discussion of how this phenomenon can be employed in a catalytic system followed by select examples in which Lewis acid – Lewis base adducts formed through n→σ* interactions have successfully been utilized in catalytic systems.

Consider the Lewis acid antimony pentachloride and Lewis base tetrachloroethylene carbonate, the donor-acceptor adduct of which has been studied crystallographically (Figure 3).[13] A lengthening of the carbonyl C=O bond is observed as electrons "pileup" on the carbonyl oxygen. As a result of this increased positive charge, a bond shortening of the C-O σ-bond is observed to compensate for the increased positive charge. Critically, when examining the bond lengths of the Lewis acid, a similar lengthening of the Sb-Cl σ-bond is observed – a result of the "spill-over" effect. The increased electron density on the acceptor is compensated for by increasing electron density on the electronegative ligands. The ultimate, and catalytically relevant, result is a Lewis acid that is *more* electropositive than prior to adduct formation. The impacts electronic redistribution are perhaps more striking when examined computationally.

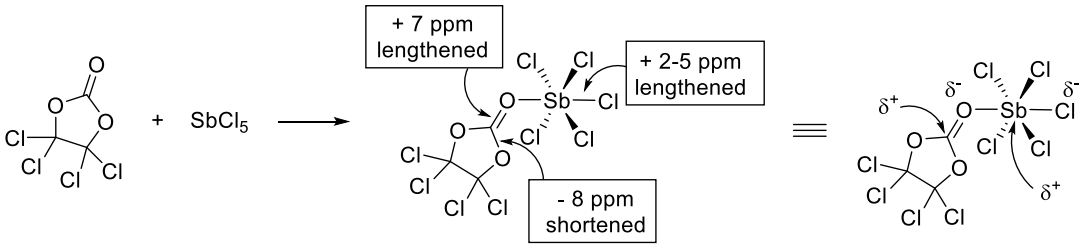


Figure 3. Lewis base-Lewis adduct structure highlighting changes in bond length and polarization.

The structures of several silicon dianions were studied computationally by Gordon and coworkers and summarized below is the stepwise interaction of silicon tetrachloride with two chloride anions (Figure 4).[16] To the far left of the equilibrium a small polarization of the Si-Cl σ bond exists with a partial positive charge residing on Si. Upon association with an exogenous chloride donor, and expansion of the silicon coordination sphere, an increase in the partial positive character of silicon is observed. These results are consistent with those seen crystallographically. Further expansion of Silicon's valance to $SiCl_6$ enhances this effect.

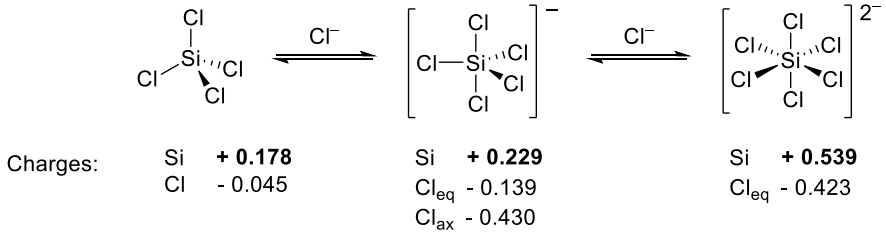


Figure 4. Calculated partial charges of Silicon during adduct formation.

This counterintuitive charge redistribution is best explained from an atomic and molecular orbital perspective.[11] The association of the anionic chloride Lewis base leads to the formation of a pentacoordinate, hypervalent siliconate. Requisite for this bond forming event is a rehybridization the silicon atom – from sp^3 to sp^2 – and the formation of a pure p-orbital. Association of a second donor results in a subsequent rehybridization event – this time from sp^2 to sp at the central silicon atom – and the formation of another pure p-orbital. These hypervalent bonds are by nature electron poor at the central atom affording the counterintuitive result of a *more electropositive* Lewis acid despite increased overall charge.

A more general treatment of this electron redistribution can be obtained by examining the newly formed molecular orbitals of three center, four electron (3c, 4e) σ-bond consisting of: the Lewis base donor (D), the central Lewis acid (M) and a ligand (L) (Figure 5).[17–19] The four electrons, two from the donor lone pair and two from M-L σ-bond populate the bonding (ψ^1) and the nonbonding (ψ^2) orbitals. Notably, ψ^2 contains a node a the central atom of the 3c,4e bond resulting in a polarization of the electrons away from the central atom and towards the peripheral ligands.

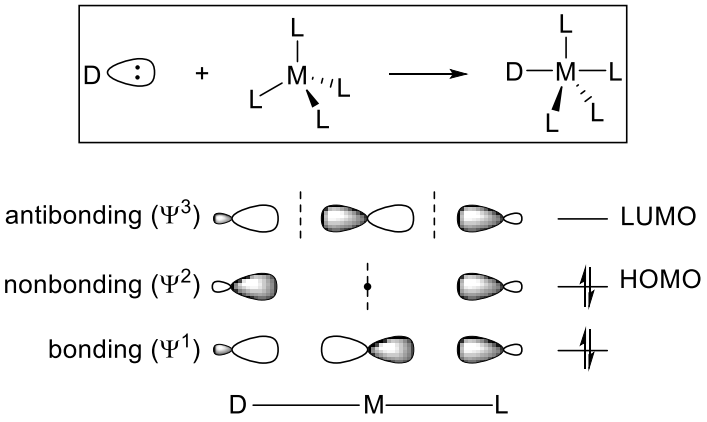


Figure 5. Molecular orbital diagram of a (3c,4e) bond.

As the M-L σ-bond becomes more polarized, the energy differential between ψ^2 and ψ^3 will increase. In the extreme scenario, a full dissociation of the ligand occurs resulting in the formation of a cationic complex (Figure 6). It is the formation of this ionized complex that has been the keystone of the pioneering work in the Denmark laboratories utilizing n→σ* activation of Lewis acids.[20]

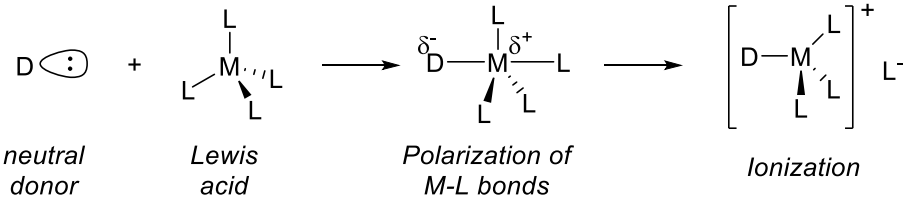


Figure 6. Formation of a cationic complex from a Lewis base-Lewis acid adduct.

Significant efforts toward the Lewis base activation of Group 14, 16 and 17 Lewis acids have been made in the Denmark laboratory. For the sake of scope and brevity, only the efforts towards Group 16 activation will be discussed below.

The ability of Group 16 electrophiles to engage in alkene functionalization has been known for decades; however, the enantioselective functionalization of alkenes remained a challenge.[21] Foundational work from the Denmark laboratories demonstrated that, when paired with an appropriate electron withdrawing ligand, Group 16 Lewis acids react analogously to Group 14 and 17 Lewis acids in the presence of a Lewis base.[22] A number of sulfur(II) Lewis acids have been shown to successfully engage in catalytic functionalization of alkenes, including those derived from phthalimide, benzotriazole, and saccharin – generally referred to as 'Sulfenylating agents'. In an analogous fashion to Figure 6, a catalytic Lewis base forms a complex with the Sulfur(II) electrophile which subsequently undergoes ionization to form a catalytically active, cationic complex – the mechanism of which has been extensively studied and is summarized below (Figure 7).[23]

Activation of sulfenylating agent **1a** by protonation with MsOH (or similar Brønsted acid) facilitates sulfur transfer to selenophosphoramide Lewis base catalyst **2** to form cationic species **3**. Subsequent transfer of the sulfenyl group to the alkene results in enantioselective thiiranium ion formation (species **4**). Stereospecific, nucleophilic capture and subsequent deprotonation affords the thiofunctionalized product **5** and regenerates the catalyst **2**.

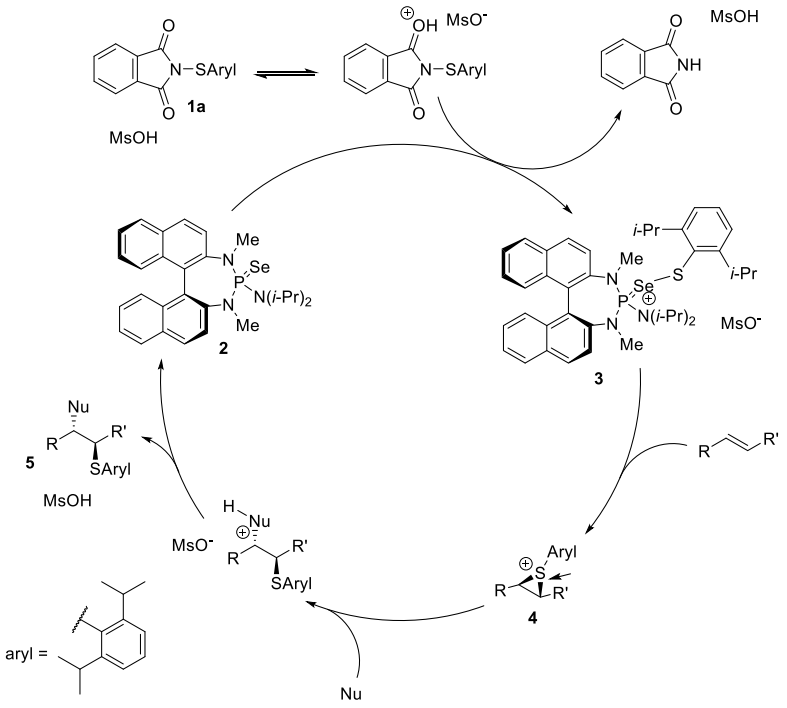


Figure 7. Mechanism of Lewis base-catalyzed, enantioselective sulfenofunctionalization of alkenes.

Methanesulfonic acid has been successfully employed to promote the catalytic, enantioselective formation of thiiranium ions which have been intercepted intramolecularly by a number of pendant nucleophiles. These include oxyfunctionalziation with alcohols and phenols, aminofunctionalization with tosylamines and tosylanilines, as well as carbofuntionalization with electron-rich arenes (Figure 8).

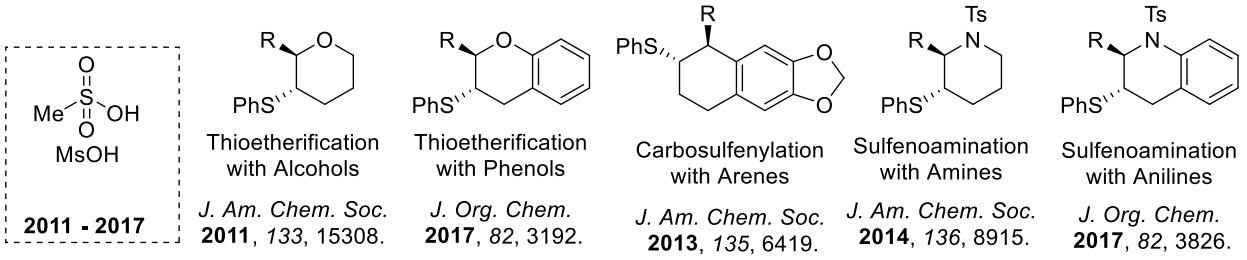


Figure 8. Transformations performed using methanesulfonic acid in dichloromethane.

An effort to effect a polyene functionalization initiated by thiiranium ion formation was initially unsuccessful employing MsOH as a Brønsted acid in dichloromethane. During a solvent survey, it was found that hexafluoroisopropyl alcohol (HFIP) without the assistance of strong

acid is capable of activating the phthalimide-derived sulfenylating agent **1a** (as noted by its characteristic change from a colorless to yellow solution and later ^{31}P NMR spectroscopy) to form the cationic Lewis acid-Lewis base complex **3**.[24] This surprising result stands in stark contrast to the belief that a strong acid is required to initiate this process. The explanation as to why HFIP (and other protic solvents) are capable of promoting the activation of the sulfenylating agent is still speculative; however, it is believed that the ability of HFIP to form a hydrogen bonding network, as well as to stabilize positive charge, is key.

Nevertheless, this discovery has enabled a significant expansion in the types of transformations that can be accessed using this chemistry. In the intervening years, not only was the polyene cyclization realized, but also carbosulfenylation via a boronate migration[25] – this time employing methanol – as well as a cascade sulfenoacetalization (Figure 9).[26] The following chapter details efforts to capitalize on this advance in the development of an inetermolecular sulfenoamination.

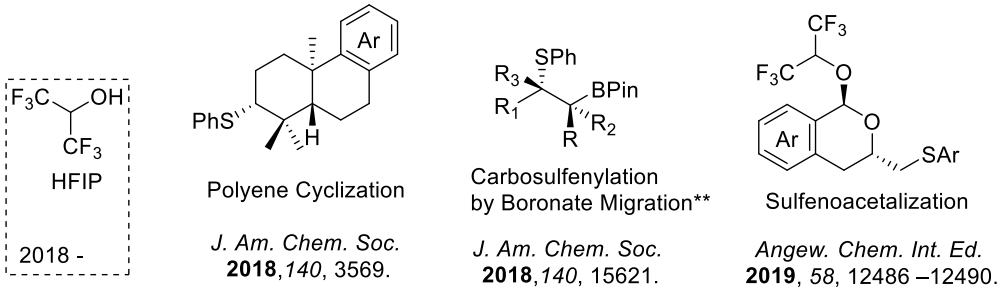


Figure 9. Transformations performed using protic solvents.

Chapter 2. Enantioselective, Lewis Base-Catalyzed, Intermolecular Sulfenoamination

2.1. Background, Prior State-of-the-Art, Research Objectives

The transformation of simple alkenes into chiral, non-racemic, vicinally functionalized building blocks serves as an important strategy for the production of value added chemicals. In the past 30 years, numerous approaches to alkene difunctionalization such as epoxidation, dihydroxylation, aminohydroxylation and halofunctionalization have been reported.[27–31] On the other hand, the sulfenofunctionalization of alkenes proceeding through racemic thiiranium ion intermediates has been known since the early 1960's, but enantioselective variants are significantly less developed. Despite their high reactivity, thiiranium ions are configurationally stable at low temperature and readily intercepted stereospecifically with various nucleophiles to afford anti-sulfenofunctionalized products.[32]

The intermolecular functionalization of thiiranium ions, pioneered in 1982 by Trost, involves formation of a racemic thiiranium ion (generated from dimethyl(methylthio)sulfonium tetrafluoroborate (DMSTF)) which then undergoes invertive opening (Figure 10, entry 1).[33] A variety of nitrogen-based nucleophiles afford the sulfenoamination products including amines, azide and nitrite nucleophiles to provide the amino, azido, and nitro sulfides, respectively. Brownbridge subsequently reported the treatment of alkenes with phenylsulfenamides in dichloromethane to access 1,2-amino thiols in moderate yields and, when in the presence of acetonitrile, the corresponding amidines are formed (Figure 10, entry 2).[34] Enders described a multistep synthesis to access a diverse array of *anti*-1,2-sulfanyl amines.[35] Key steps include a diasteroselective α-alkylation of α-sulfanylated acetaldehyde-SAMP-hydrozones followed by a 1,2-addition of various organocerium nucleophiles. The corresponding hydrazines could be converted in good yields and diastereoselectvives to the desired *anti*-1,2-amino thiols. In the intervening years a number of methods have been disclosed to access racemic 1,2-amino thiols including trifluoromethylthioamination of alkenes catalyzed by diaryl selenides reported by Zhao et. al. and a highly efficient electrochemical oxy- and aminosulfenylation of alkenes by Yuan et. al. [36,37]

Indeed, strategies to access enantiomerically enriched 1,2-amino thiols have largely relied on the desymmetrization of aziridines.[38] In contrast, the formation and functionalization of enantioenriched thiiranium ions has been significantly less explored. In 1994 Rayner reported the synthesis of benzoxazines by the intramolecular capture of thiiranium ions generated from

enantiomerically enriched sulfenyl sulfonium salts.[39] Although the products are obtained in acceptable yield, enantioinduction was poor, ostensibly from substrate-mediated background reaction. In the same year, Pasquato et al. disclosed the first enantioselective intermolecular sulfenoamination achieved through an enantioenriched thiiranium ion intermediate (Figure 10, entry 3).[40] A stoichiometric quantity of a chiral dinaphtho[2,1-c:1',2'-e][1,2]dithiin sulfenylating agent produces enantioenriched thiiranium ions which undergo capture with acetonitrile in a Ritter-type process to provide the corresponding sulfeno acetamides in good yield and enantioselectivity.

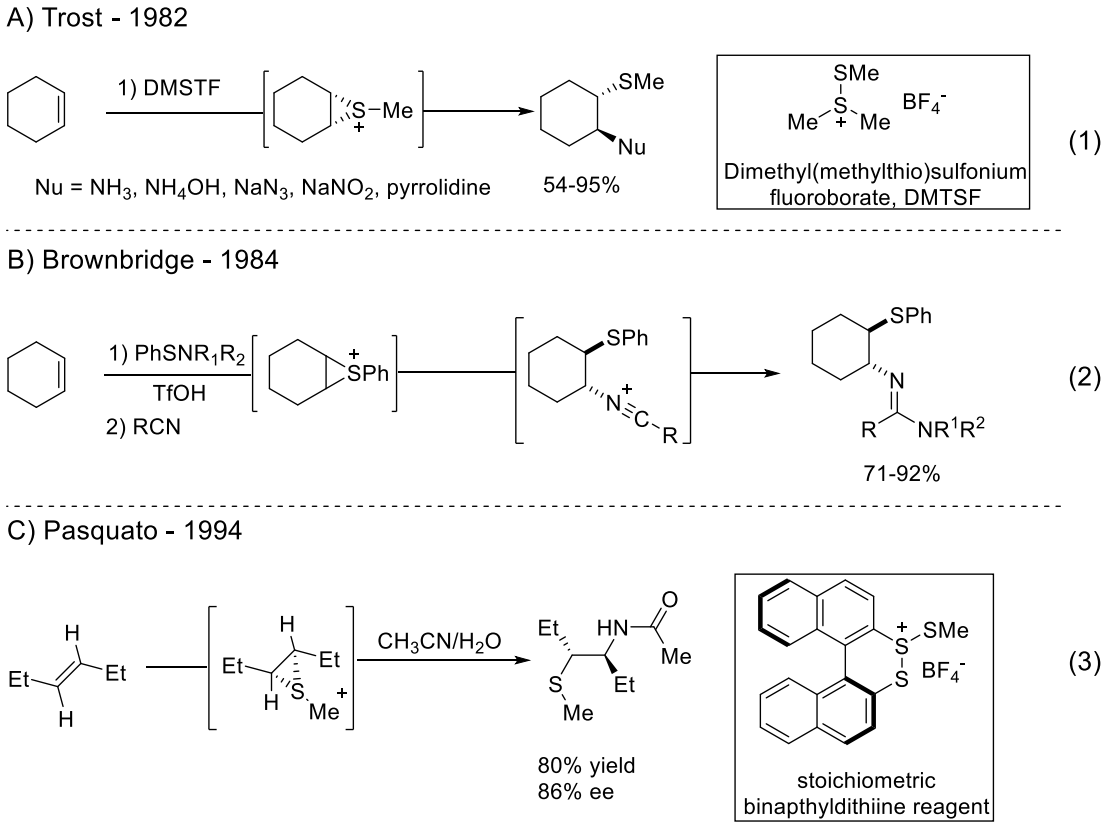


Figure 10. Previous intermolecular sulfenoaminations from thiiranium ions.

Furthermore, the 1,2-amino thiol motif can be found in a number of medicinally relevant small molecules (Figure 11). These include penicillin-derived antibiotics, β-lactamase inhibitor aulbactam, psoriasis treatment apremilast, as well as biotin – a common dietary supplement. Notably all of these examples not only bear a 1,2-aminothiol moiety but bear stereogenic centers with an *anti*-relationship at these positions. Given that methods to rapidly access these types of

vicinal stereocenters are lacking, developing an intermolecular capture of a thiiranium ion with an amine nucleophile was seen as an important objective.

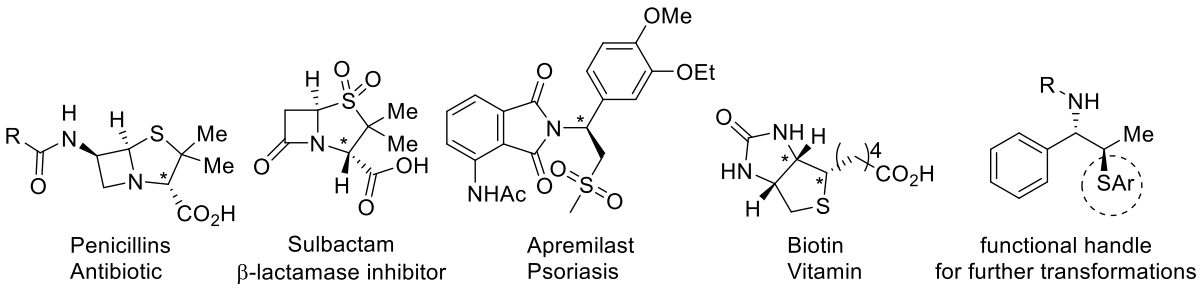


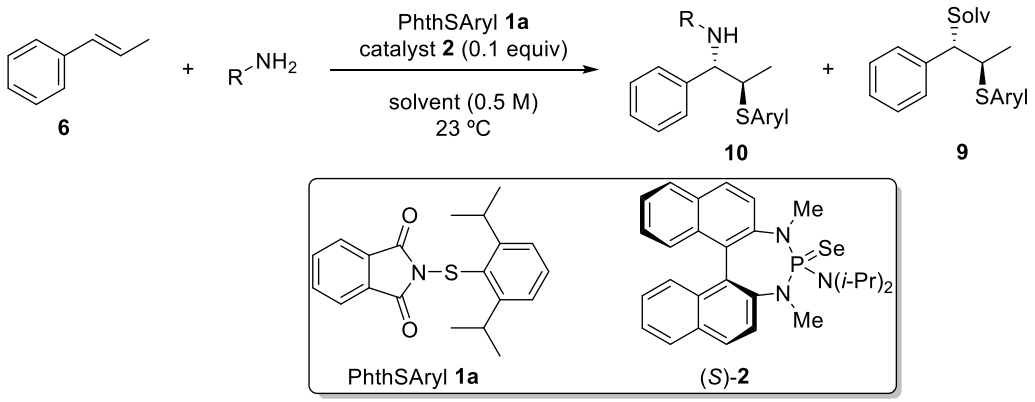
Figure 11. Select natural products and synthetic compounds with 1,2-aminothiol motifs.

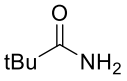
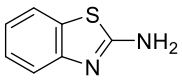
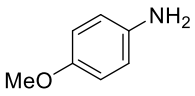
A second, and perhaps more general goal of this project, was to identify a method to readily use the thio ether moiety as a functional group handle to perform product manipulations. Previous studies readily demonstrated that under forcing conditions, a phenylthio ether can undergo elimination subsequent to oxidation to form alkenes as well as ketone under Pummer-type conditions.[24] It was anticipated that similar types of reactivity would be accessible to the 1,2-amino thiol motif, albiet requiring less forcing conditions, to provide a diverse array of enantioenriched, thiofunctionalized products.

2.2. Reaction Development

Orienting experiments (Table 1) initially employed HFIP (0.5 M), (*E*)-2-methylstyrene **6**, sulfenylating agent **1a** (1.0 equiv), catalyst (*S*)-**2** (0.1 equiv) or tetrahydrothiophene **7** (THT, 0.1 equiv) and *p*-tolulenesulfonamide **8** ($TsNH_2$, 1.0 equiv) as the nucleophile. Unfortunately, only the oxysulfenylated product **9** corresponding to solvent incorporation was observed. The same result was observed when the comparatively less nucleophilic nonafluoro-*tert*-butyl alcohol (9F-t-BuOH) was employed. The use of mixed solvent systems (dichloromethane/HFIP, dichloromethane/9F-*t*-BuOH and toluene/9F-*t*-BuOH) failed to provide the desired products, resulting in the generation of side products. At this point it was deemed prudent to survey several amines that could intercept the thiiranium ion more readily than HFIP. Nucleophiles such as *tert*-butyl carbamate and 2-aminobenzothiazole again afforded the oxysulfenylated product **9**. Gratifyingly, *p*-anisidine was identified as an effective nucleophile and no solvent incorporation was observed to afford **10**.

Table 1. Reaction optimization.



entry	nucleophile	solvent	10	9
1	$TsNH_2$	HFIP	0%	76%[a]
2	$TsNH_2$	9F-*t*BuOH	0%	67%[a]
3	$TsNH_2$	9F-*t*BuOH/ DCM	0%	0%[c]
4	$TsNH_2$	9F-*t*BuOH/ toluene	0%	0%[c]
5		HFIP	0%	81%[b]
6		HFIP	0%	79%[b]
7		HFIP	73%[a]	0%

(a) isolated yield (b) NMR yield (c) unidentified side products were formed

Reaction conditions were further refined through the use of Design of Experiment (DoE) software.[41] Multivariate optimization stands apart from the more traditional univariate optimization in that multiple reaction parameters are changed in order to examine the interplay of these changes. This approach has a number of advantages over univariate optimization. Perhaps most significantly employing a DOE protocol results in a more efficient process optimization.[42] Additionally, univariate approaches do not find a true "optimal" process because this method is highly dependent on starting point. This true optimum is also aided by employing DoE by eliminating researcher bias and run-to-run variation that may be interpreted as an improvement in reaction outcome.[42]

To optimize the intermolecular sulfenylamination, four reaction factors were examined in this protocol: overall concentration, equivalents of both sulfenylating agent **1a** and *p*-anisidine, as well as catalyst loading. A D-optimal design was selected and a total of twenty-five experiments were conducted and the results were analyzed by ^{1}H-NMR spectroscopy and a response surface was generated. Results were fitted to a quadratic model to generate a response surface model which was validated through two different point-prediction conformations.

When examining the original conditions (Figure 12, 1.0 equiv of both *p*-anisidine and sulfenylating agent **1a** with 10 mol% (*S*)-**2** at 0.5M in HFIP) the model predicted that the yield of the resulting reaction should be approximately 75%. Previous experiments, which provided an isolated yield of 73%, correlated well with the model. This step was crucial in validating the model as DoE predictions are predictions and must be validated once, if not more.[42]

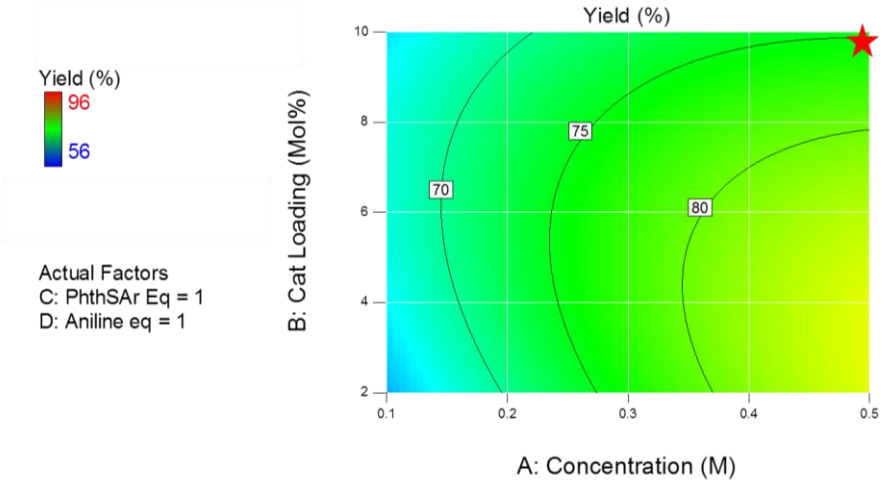


Figure 12. DoE predicted response surface of initial conditions.

Figure 13 shows a representative contour plot examining the effect of changing equivalents of sulfenylating agent **1a** and *p*-amisidine on yield while maintaining concentration (0.5M) and catalyst loading (5 mol %) constant. A slight excess of sulfenylating agent **1a** (1.2 equiv) and *p*-anisidine (1.6 equiv) were required because sulfenylation of the *p*-anisidine to form the corresponding thiohydroxylamine was identified as a parasitic byproduct.

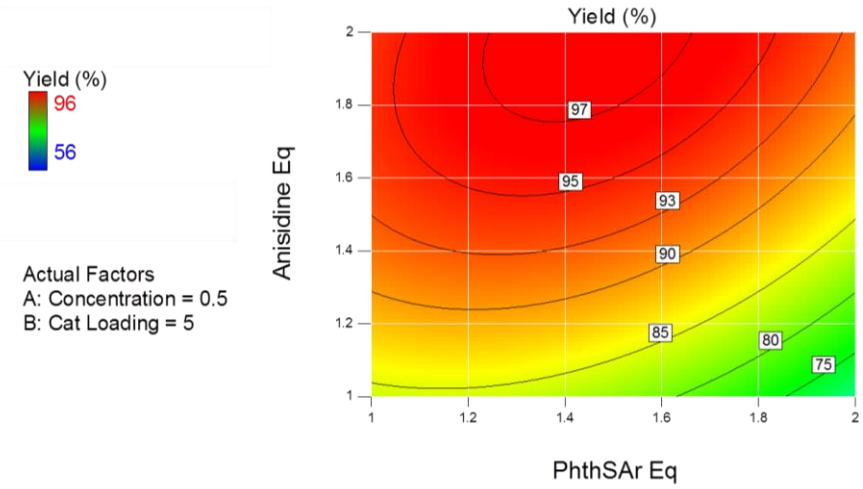


Figure 13. DoE predicted response surface showing relationship of nucleophile and sulfenylating agent.

Examining the effects of reaction concentration and nucleophile equivalents on yield shows a dependence on both (Figure 14). When concentration was reduced, an increase in oxysulfenylated product **9** was observed from solvent incorporation. A slight excess of nucleophile increased the yield slightly be avoiding the same oxysulfenylated byproduct. Lastly, reactions run for 24 h at ambient temperature maintained high yields with catalyst loading as low as 5 mol %.

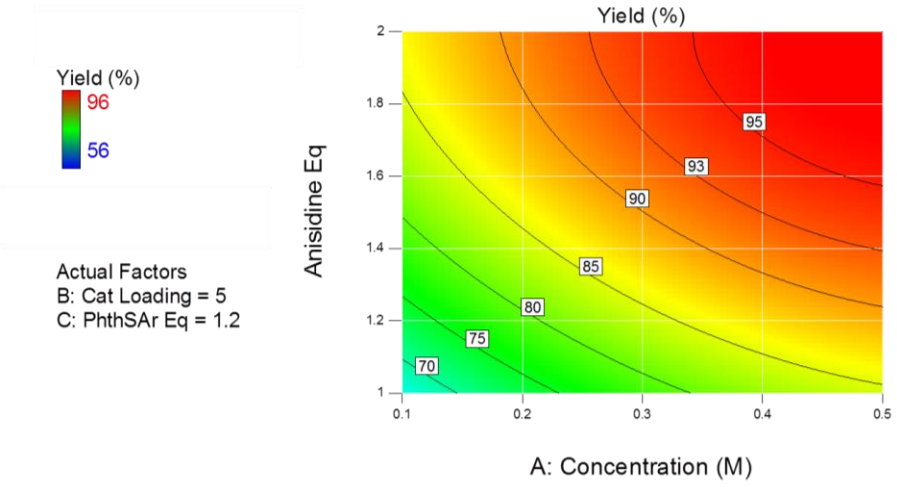
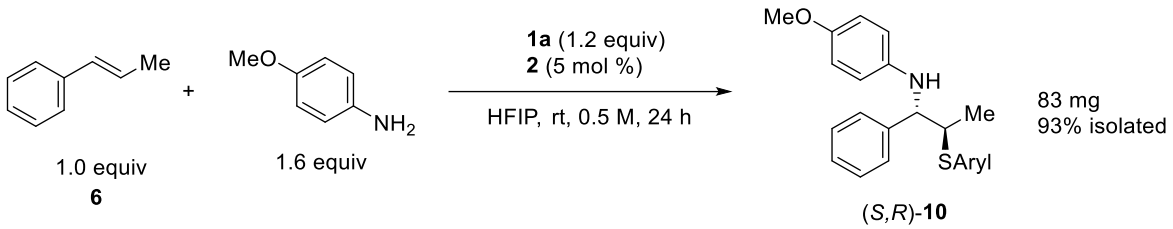


Figure 14. DoE predicted response surface showing relationship of nucleophile and sulfenylating agent with validation experiment.

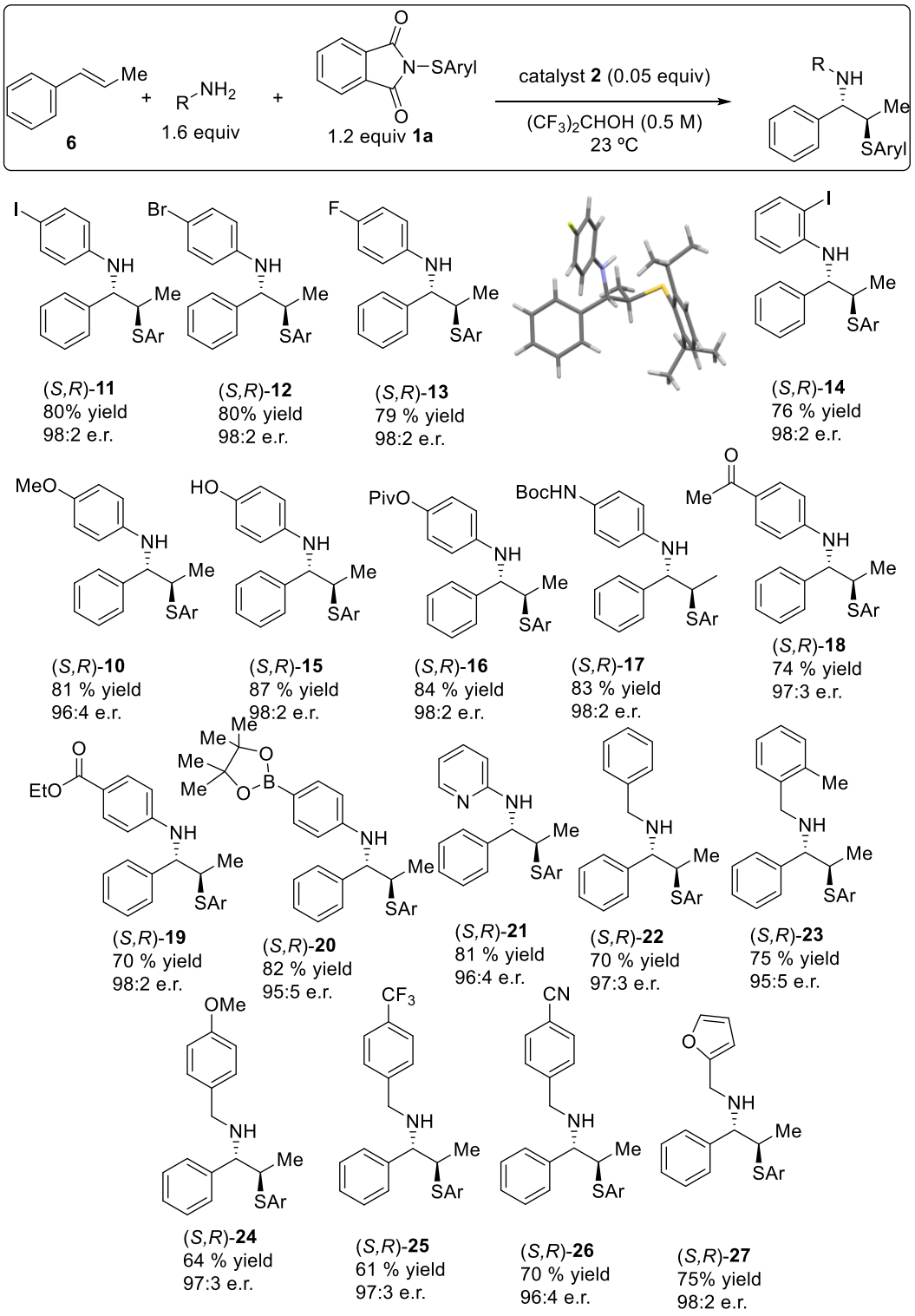
These conditions were again tested to verify the authenticity of the model and corresponded well with the predicted values (Scheme 1). The optimized conditions were used to evaluate a number of olefins and nucleophiles in the enantioselective, intermolecular sulfenoamination.

Scheme 1. Intermolecular sulfenoamination of β-methyl styrene.



2.3 Reaction Scope

Under the optimized conditions, a number of anilines containing both electron donating and electron withdrawing functional groups were evaluated. 4-Haloanilines were competent, affording the corresponding aminofunctionalized products **11**-**13** as single diastereomers in good yield and 98:2 enantiomeric ratio. The absolute configuration of the product was confirmed by single crystal X-ray diffraction and corresponds to the selectivity models previously described.[23] 2-Iodoaniline was incorporated in good yield and high enantioselectivity was maintained. Electron-rich anilines were also incorporated giving products **10** and **15** in good yield. Owing to the mild conditions enabled by HFIP, acid-labile protecting groups are compatible as demonstrated by synthesis of pivalate **16** in 84% yield and carbamate **17** in 83% yield. Of note is the ability of electron deficient anilines to outcompete the formation of oxysulfenylated product. 4-Aminoacetopheone and benzocaine were cleanly incorporated to afford products **18** and **19** respectively in good yield. 4-Aminophenylboronic acid pinacol ester provided the desired product **20** in 82% yield and thereby provides an additional functional group for subsequent cross coupling reactions. 2-Aminopydridine was also competent affording **21** in good yield and selectivity.

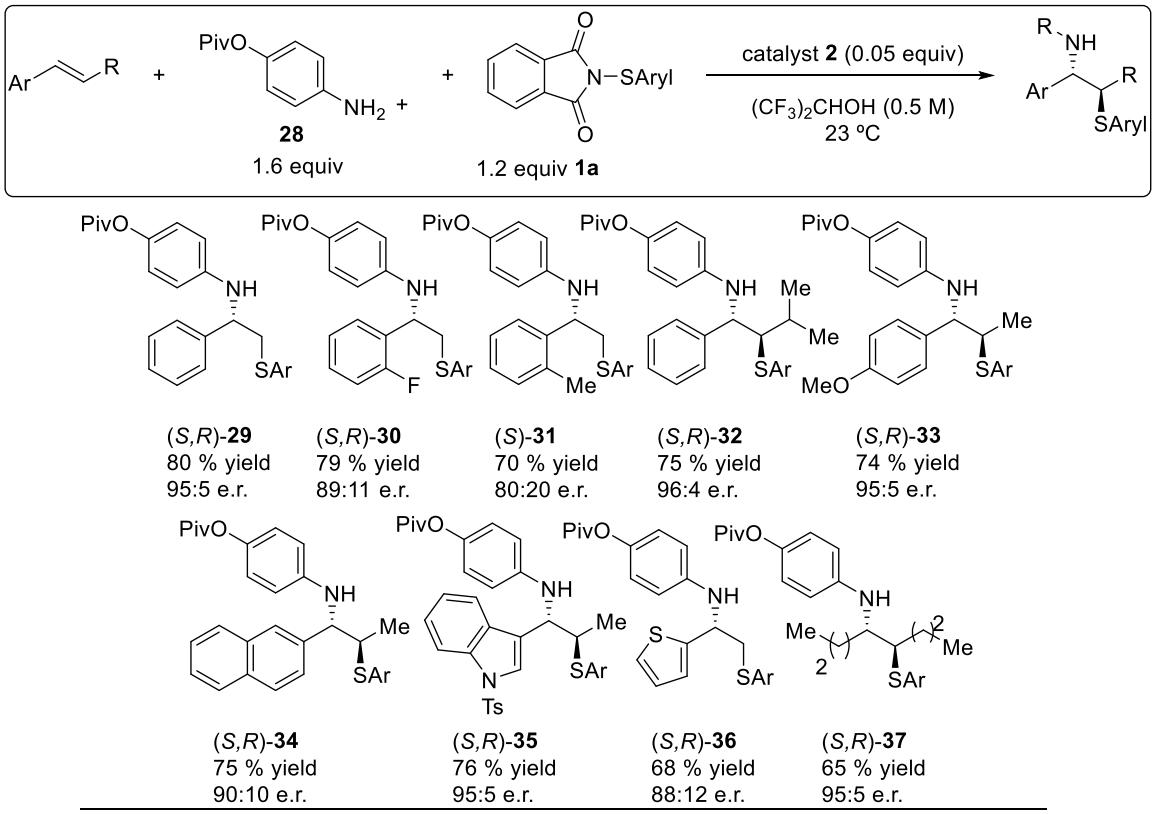


a All reactions performed on a 1.00 mmol scale. b Yield of isolated, analytically pure product.
c Determined by CSP-HPLC or CSP-SFC analysis.

Figure 15. Scope of nucleophiles in sulfenoamination.

The method was extended to a number of benzylic amine nucleophiles. Benzylamine was incorporated efficiently as was 2-methylbenzylamine to give the corresponding products **22** and **23** in 70% and 75% yield respectively with no appreciable loss in enantioselectivity. Benzylamines containing the inductively withdrawing and resonance withdrawing trifluoromethyl and 4-cyano substituents reacted efficiently to give **25** and **26**. 2-Furfurylmethylamine was smoothly incorporated in 75% yield and 98:2 e.r.

With respect to the olefin scope, styrene, which had previously given poor results in the presence of strong acid, was readily functionalized in 80% yield and 96:4 e.r. Additionally, products **30** and **31** arising from 2-fluorostyrene and 2-methylstyrene respectively were obtained in synthetically useful yields; however, both suffered from slight degradation in selectivity. 1-(3-Methyl)butenylbenzene reacted to afford **32** in good yield and selectivity. Similarly, anethole is also capable of efficient cation stabilization which might result in a mixture of diastereomers. Gratifyingly, anethole was competent in the reaction providing the desired product **33** in 74% yield and 95:5 e.r. Difunctionalized products containing extended aromatic systems (**34**), N-tosyl substituted indole (**35**), heterocycles (**36**) and aliphatic alkenes (**37**) were all produced in good yield and good to excellent selectivity.



a All reactions performed on a 1.00 mmol scale. b Yield of isolated, analytically pure product.
c Determined by CSP-HPLC or CSP-SFC analysis.

Figure 16. Olefin Scope.

2.4. Mechanism, Site Selectivity and Limitations

From previous mechanistic investigations, a catalytic cycle is proposed in Figure 17.[23,43] Activation of sulfenylating agent **1a** by protonation with HFIP facilitates sulfur transfer to selenophosphoramide catalyst **2** to form cationic species **38**. Subsequent transfer of the sulfenyl group to the alkene results in enantioselective thiiranium ion formation (species **4**). Stereospecific, intermolecular nucleophilic capture and subsequent deprotonation affords the vicinally functionalized product **39** and regenerates the catalyst.

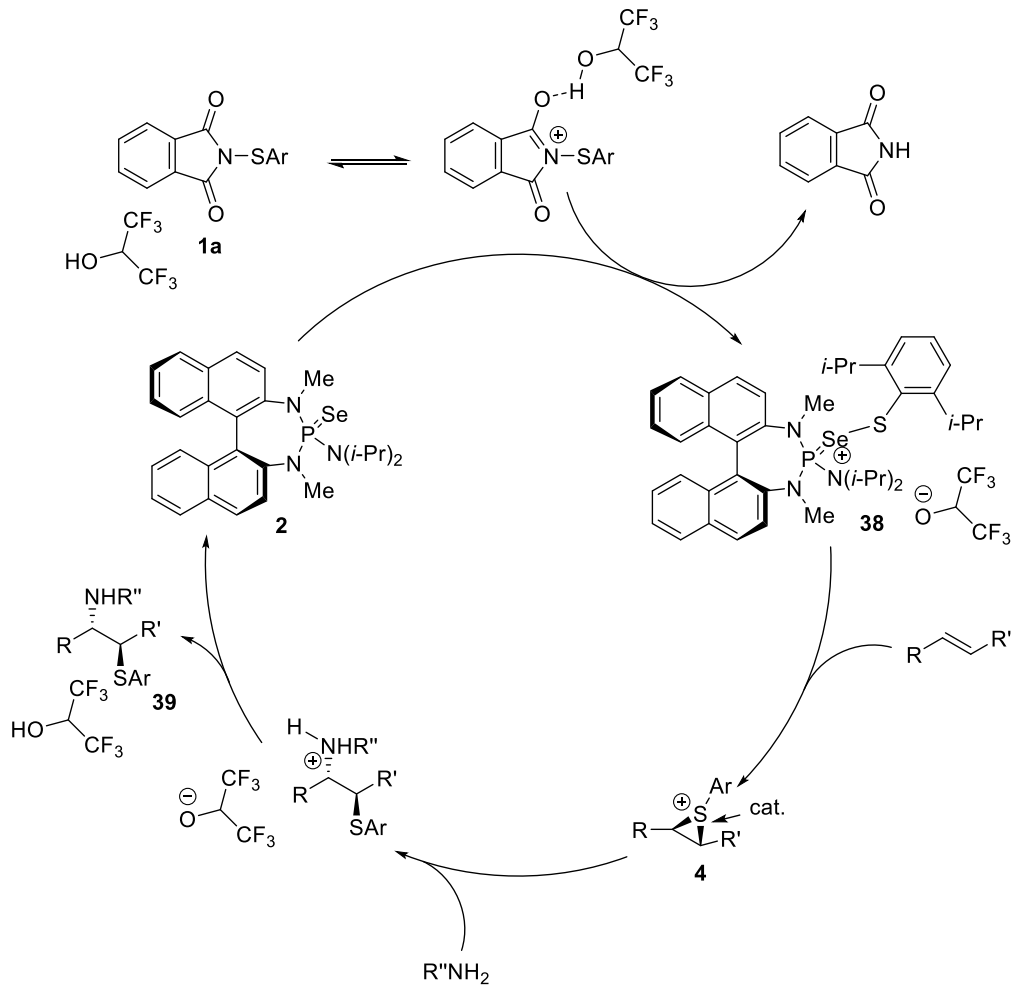


Figure 17. Proposed catalytic cycle.

Any synthetic method will have limitations and, given the nature of intermolecular capture, it is feasible that constitutional isomers might arise from stereospecific, nucleophilic opening of the thiiranium ion at the two different C-S centers. Olefins bearing arenes provided exclusively one constitutional isomer owing to the stabilization of the positive charge at the benzylic position during the ring opening. The same selectivity was seen with oxysulfenylation product **9** as well. Aliphatic substrates did not enjoy this biased selectivity. Aminosulfenylation of 1-heptene resulted in a complex mixture which provided constitutional isomers **40** and **41** in a 1:1 ratio. Attempts to bias selectivity electronically using (allyloxy)benzene were unsuccessful owing to the decreased nucleophilicity of the alkene. Indeed, this reaction proved quite sensitive to the electronic nature of the double bond and as one might anticipate, very electron deficient 1-(trifluoromethyl)-4-vinylbenzene failed to furnish the desired product **42**, owing to the decreased

nucleophilicity of the double bond. Additionally, stilbene failed to react to provide **43** owing to poor solubility of the starting material in HFIP.

Attempts to functionalize α-methylstyrene afforded the desired sulfenofunctionalized product **44** in low yield and, unfortunately, in racemic form. This outcome likely arises from the intermediacy of a stabilized, open carbocation rather than by stereospecific ring opening of a thiiranium ion. Although 2-aminopyridine was readily incorporated, 4-aminopyridine failed to provide the desired product **45** but rather afforded exclusively the oxysulfenylated product **9** obtained through solvent incorporation. This unfortunate, yet somewhat ironic, result comes about as a result of 4-aminopyridine forming the corresponding cationic pyridinylium, which undergoes thiiranium ion reformation, and is subsequently captured by HFIP.

One additional side product that was encountered was a second sulfenylation of the product. This side product was observed in a number of sulfenoaminations and was particularly problematic when employing aniline as the nucleophile, where **46** and **47** were observed in a 55:45 ratio. The same deleterious, inseparable side product was observed when employing 1-naphthylamine. This problem continued when electron rich, sterically encumbered nucleophiles were employed. *m*-Anisidine when subjected to the reaction conditions returned the desired product **48** and **49** in a 67:33 ratio while *o*-anisidine failed to provide **51** but was exclusively C-sulfenylated to afford **51**. This type of reactivity is known and has been reported previously.[44]

On initial evaluation, incorporation of aliphatic amines was largely unsuccessful owing to their increased Brønsted basicity (leading to protonation under these conditions) resulting in the formation of the oxysulfenylation product **9** exclusively rather than desired amino thiols. When employing (*R*)-α-methyl benzylamine as the nucleophile, a 70% NMR yield of **52** was observed whereas isoamyl amine afforded product **53** in 40% NMR yield – likely an effect of the increased Brønsted basiscity and β-branching. Isopropylamine formed the resulting product **54** in a paltry 10% yield. This outcome may be improved by increasing the equivalents of amine but was not attempted. Similarly, morpholine was examined as a nucleophile but did not return a significant amount of the desired product **55**. These experiments show a clear and apparent trend between yield and pK_b. As the pK_b of the nucleophile increases, the ratio between protonated, non-nucleophilic ammonium species is increased, and the yield of the desired product decreases.

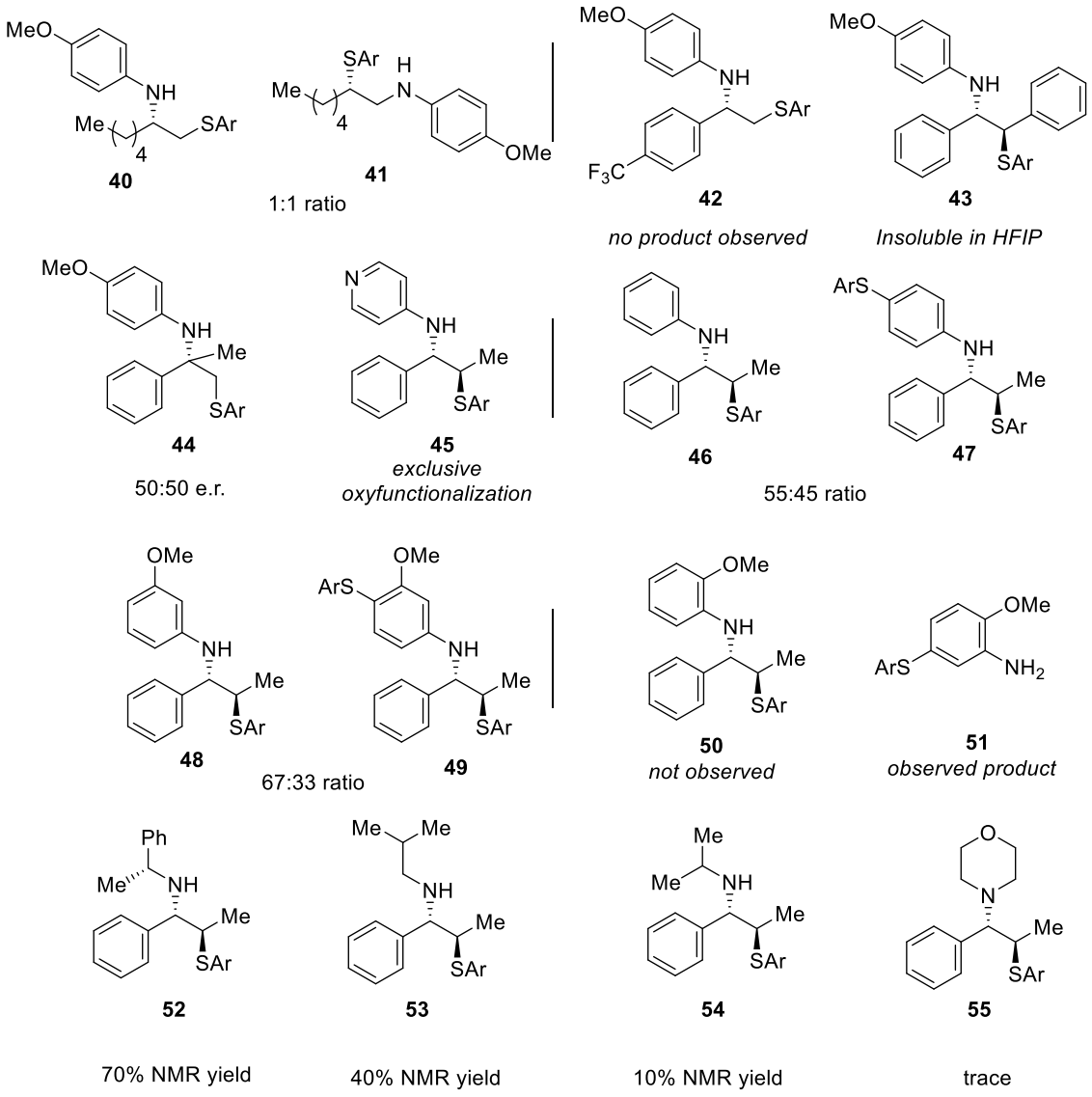


Figure 18. Failed intermolecular functionalization substrates and nucleophiles.

2.5. Product Manipulations

A major objective of this project was the subsequent derivatization of the sulfenofunctionalized products. Although the increased steric bulk of the 2,6-diisopropylsulfenylating agent **1a** affords superior enantioselectivities, this same property reduces reactivity of the thio ether and complicates subsequent functionalization. Indeed, previous successful examples of functionalization of the 2,6-diisopropylphenyl thio ether are

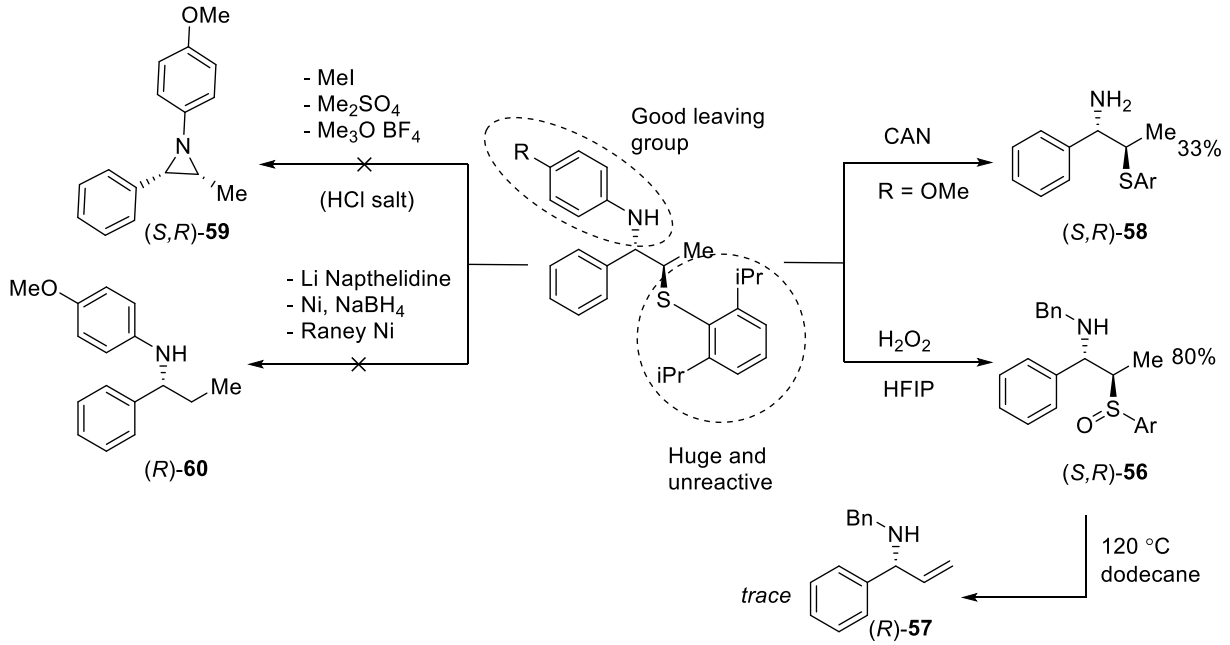
largely limited to oxidation-Pummer sequences.[24] All others employ either harsh reaction conditions or the phenylthio ether derivative.

Initial attempts to transform the aminofunctionalzed products into useful motifs were met with limited success. Treatment of **10** with H_2O_2 in HFIP, a protocol designed to give exclusively the sulfoxide, failed when in the presence of the electron rich arene; however, this was successful by changing to the benzylamine derived **22**. Ultimately, despite surveying temperature and additives, thermal elimination gave poor yields of the allyl amine **57** which can be readily accessed employing alternative methods.[45] Oxidative cleavage of the *p*-aniside to afford the free amine **58** required significant optimization. At room temperature significant decomposition of the starting material was observed; however, at cryogenic temperatures (below -50 °C) sluggish reactivity was observed. Ultimately it was found that a two-step protocol was required to liberate the free amine **58**. First, careful oxidation of the anisidine moiety with ceric ammonium nitrate (CAN) at -50 °C provided the requisite intermediate for hydrolysis. Hydrolysis was found to be sluggish at room temperature and ultimately, heating to 40 °C in the presence of HCl afforded the free amine **58** in poor yield.

In an attempt to form an aziridne **59** through an S-methylation-intramolecular displacement protocol, a number of methylating agents were surveyed. However, subjecting **10**, which had been protected as the HCl salt, to iodomethane, dimethyl sulfate and trimethoxonium tetrafluoroborate all failed to provide the requisite sulfonium ion! The challenge of performing seemingly simple chemistry with the thio ether speaks to the highly encumbered steric environment arising from the presence of the 2,6-diisopropylphenyl moiety.

Endeavors to cleave the C-S bond to remove the bulky arylthio ether were equally as challenging. Treatment of **10** with Raney nickel in refluxing ethanol returned only starting material. The same result was obtained with *in situ* generated nickel boride in refluxing ethanol. Attempts to perform a magnesium-sulfoxide exchange on sulfoxide **56** also returned starting material.

Scheme 2. Attempted product manipulations.



Careful reexamination of reaction conditions led to the conclusion that an alternative mechanism to cleave the C-S bond would be required. It was anticipated that a single electron reductant would prove successful in cleaving the C-S bond. This strategy had previously been employed in the Denmark Laboratory and is a very common way to cleave C-S bonds to generate the corresponding alkyl lithium species.[24] This process proceeds by generating an aryl radical anion from the corresponding arene and lithium (or other alkali metal) followed by rapid C-S bond homolysis to generate the free radical and arylthiolate. A second, rapid, reduction of the free radical generates the corresponding alkyllithium species.

When employing LiDTBB, full consumption of starting material **6** was seen, however, no productive reaction was observed. Instead, spontaneous decomposition of the anion **61** through β-elimination occurred. These β-functionalized organolithium componds are considered to be unknown species as they are unstable at or below -100 °C.[46] A potential solution was inspired by a report from Yus and coworkers, which describes the generation of stable β-amido alkyllithium species **62** through a two-step, one-pot protocol by pre-forming the lithium amide, which serves

to prevent β-elimination.[46] By placing negative charge on the putative leaving group, β-elimination is inhibited at low temperatures.

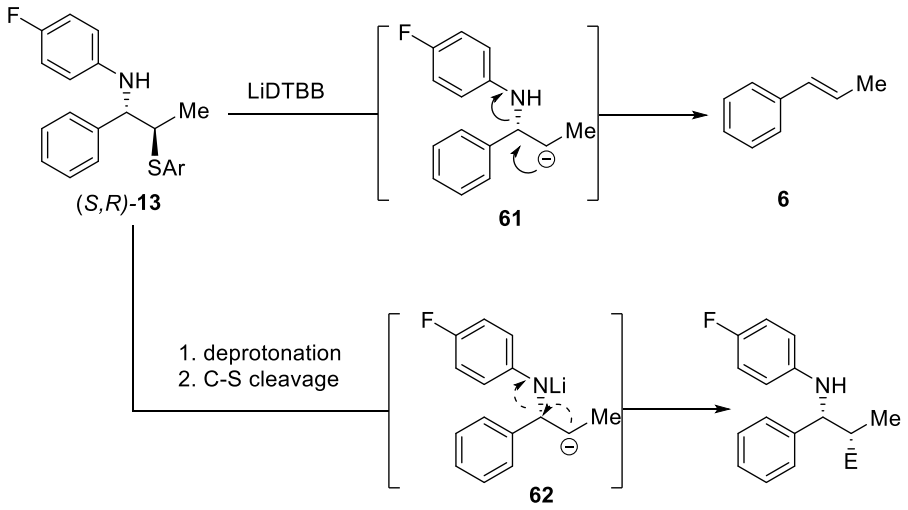


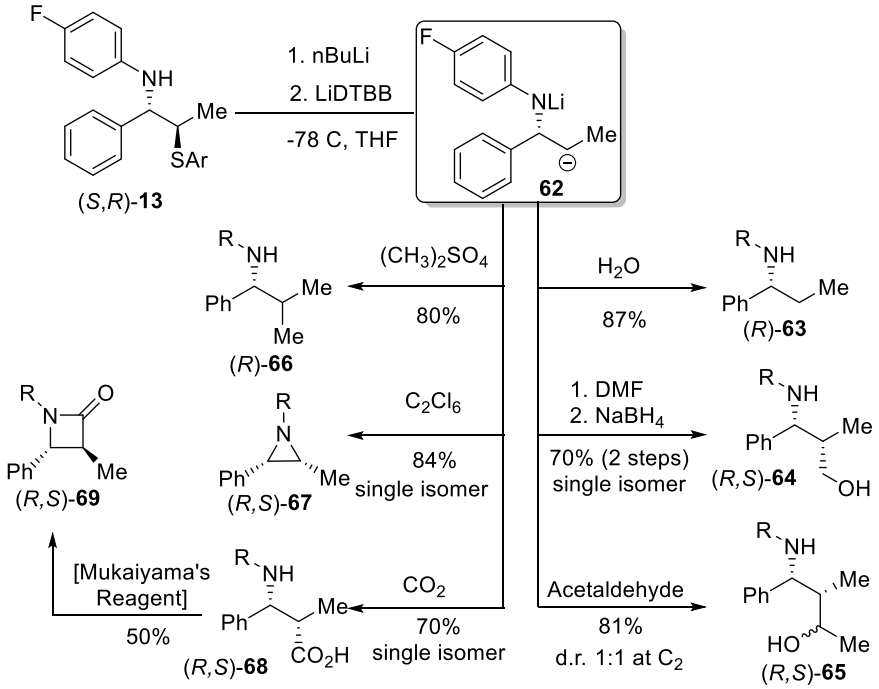
Figure 19. Two step protocol involving NH deprotonation then C-S bond cleavage.

Originally, β-amido alkyllithiums were generated via mercury-lithium transmetalation at cryogenic temperatures from the corresponding organomercury compounds.[47] Subsequent trapping of these reactive intermediates with viable electrophiles afford a number of functionalized products. This same sequence of exchange, followed by capture, has been implemented with a number of starting precursors including: organotin, halogen, activated methylenes (via deprotonation) to provide the same intermediate.[48] Of note is the use of β-amino and β-alkoxy thioethers to effect the formation of the corresponding alkyllithiums. Rather than utilizing a strong lithium base to perform the exchange, thio ethers are reduced by a single electron transfer to afford the alkyllithium species. By first deprotonating the β-leaving group, the same alkyllithium species can be formed at cryogenic temperature without the use of strong base. This protocol has been used to successfully form dianions which were subsequently captured by a number of competent electrophiles including: water, benzaldehyde and acetone. Additionally, this strategy has been employed in the total synthesis of different natural products[49–51]. The synthesis of (-)-aculeatin A employed an β-alkoxy alkyllthium generated from the corresponding phenyl thioether to intercept a Weinreb amide. In a model study, when employing excess of the alkyllithium (1.5 equiv), yields between 92% and 94% were observed.

Stoichiometric amounts of alkyllithium and Weinreb amide provided the corresponding ketone in a still acceptable 68-85%. This same reaction sequence was utilized to access (+)-neopeltolide, as well as the C1-C52 fragment of amphidinol 3.

By pre-forming the lithium amide (by deprotonation with *n*-BuLi) prior to treatment with lithium 4,4′-di-tert-butylbiphenylide (LiDTBB), the β-amido alkyllithium adduct **62** was successfully converted into a number of functionalized derivatives (Scheme 3). The desulfurized product **63** was formed in 87% yield by quenching the dianion with water whereas the 1,3-amino alcohol **64** was formed as a single diastereomer through capture with dimethyl formamide and subsequent reduction with no loss in enantiomeric purity. Reaction of **62** with acetaldehyde proceeded in good yield to provide **65** as a mixture of diastereomers whereas treatment with dimethyl sulfate afforded the C-methylated product **66** in 84% yield. Aziridine **67** was accessed via the intermediate *syn*-2-chlorolithophenyl amide (by reaction with hexachloroethane) and subsequent invertive displacement. Finally, carbon dioxide was captured to afford the syn-amino acid **68**, which was next cyclized to the β-lactam **69** after treatment with Mukaiyama's reagent.[52] The relative configurations of these adducts were established by comparison to literature values.[53,54]

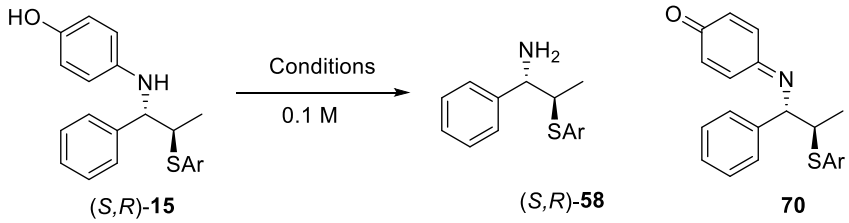
Scheme 3. Successful product manipulations.



While efficiently functionalizing the thio ether was a primary goal, it was also important to demonstrate that the primary amine can be unveiled from the aniline nucleophile. Given the challenges associated with oxidation of the *p*-anisidne derived **10**, product **15** bearing a free phenol was chosen instead. Subjecting phenol **15** to either I_2/KOH or periodic acid gave promising results furnishing **70** in 72% and 45% respectively (Table 2). However, given the challenges associated with hydrolysis, it was chosen not to pursue this avenue. Rather, attempts using hypervalent iodine reagent (Diacetoxyiodo)benzene (PIDA) gave promising results. Treatment with 2 equiv of PIDA provided the oxidized intermediate **70** in 20%. Although apparently less successful than I_2/KOH, the use of this class of hypervalent iodine reagents provided the option of adding acid to facilitate hydrolysis in a single pot. This effect is demonstrated in Table 2, entries 5 and 6 in which phosphoric acid (pKa_1 = 2.14) and trichloroacetic acid (pKa = 0.66) show greater conversion to the oxidized product, and in the latter case, formation of free amine. By employing PIFA, which will generate trifluoroacetic acid *in situ*, under the same conditions 50% conversion to the primary amine was observed. Lowering the temperature to 0 °C increased the yield to 70%. A brief solvent survey indicated that MeCN/water was the superior solvent combination as methanol, HFIP and 1,1,1,-

trifluoroethanol all failed to furnish the desired primary amine. Finally, for ease of purification, a protocol was developed in which the crude reaction mixture is treated with 1 equiv of 1 M HCl in ether to provide the HCl salt **71**.

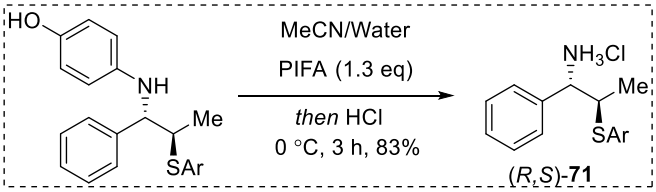
Table 2. Optimization of amine deprotection.



(*S,R*)-**15** (*S,R*)-**58** **70**

entry	oxidant	solvent	temp, °C	time, h	yields, %[1]	
					58	**70**
1	O_2, NaOH (5 equiv)	MeCN:water (1:1)	0	24	0	0 [2]
2	H_2IO_6 (1 equiv	MeCN:water (1:1)	0	1	0	45
3	I_2 (2 equiv), NaOH (5 equiv)	MeCN:water (1:1)	0	24	0	72
4	PIDA (2 equiv)	MeCN:water (2:1)	25	12	0	20
5	PIDA (2 equiv) then H_3PO_4 (5 equiv, 3 h)	MeCN:water (2:1)	25	1	0	45
6	PIDA (2 equiv) then Cl_3CO_2H (5 equiv, 3 h)	MeCN:water (2:1)	25	1	12	28
7	PIFA (2 equiv)	MeCN:water (2:1)	25	1	50	0
8	**PIFA (2 equiv)**	**MeCN:water (2:1)**	**0**	**1**	**70**	**0**
9	PIFA (2 equiv)	MeOH	0	1	0	12
10	PIFA (2 equiv)	TFE	0	1	0	80
11	PIFA (2 equiv)	HFIP	0	1	0	20

[1] Yields determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane internal standard.]
[2] No major product present by ^{1}H NMR analysis



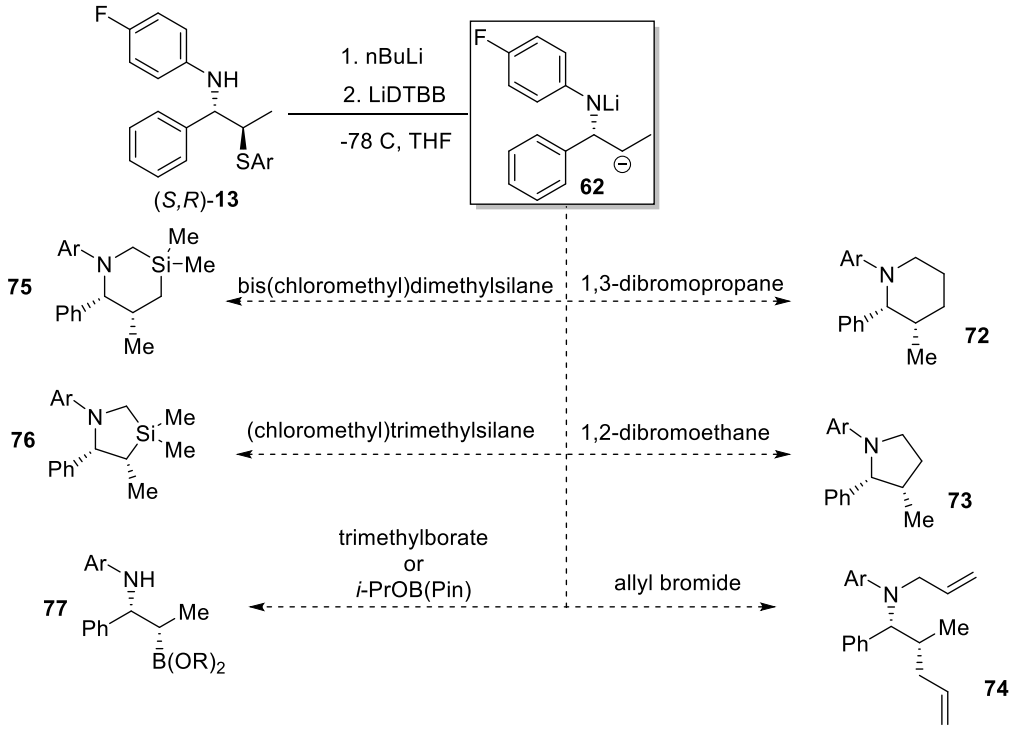
(*R,S*)-**71**

Attempts to alkylate intermediate **62** were met with little success. Employing 1,3-dibromopropane did not provide the desired product **72**, and 1,2-dibromopropane served as a

brominating agent and the corresponding aziridne **67** was recovered, rather than **73**, albeit in lower yield than with previously employed conditions. Exhaustive allylation provided the desired bisallyl product **74** in poor yield and poor 55:45 d.r. This product likely arises owing to the presence of lithium bromide generated during the reaction which disrupts a highly organized organolithium complex.

Similar failures were also seen when attempting to access silicon-containing heterocycles. Treatment of the β-amido alkyllithium intermediate **62** with (chloromethyl)trimethylsilane or bis(chloromethyl)dimethylsilane failed to provide the corresponding silazaheterocyles **75** and **76**, respectively. It is likely that decomposition of silicon-containing heterocycles proceeded through an intramolecular sila-Matteson rearrangement in which siliation of the alkyllithium was successful but, rather than S_N2 displacement of the primary chloride, a hydrolytically unstable azasiletidine was formed which spontaneously decomposed on workup. Attempts to trap with a number of other electrophiles were met with little or no success. Neither trimethoxyborate nor *i*-PrOB(Pin) provided any of the desired product **77**.

Scheme 4. Failed functionalization of β-amido alkyllithium intermediate.



2.6. Conclusions and Outlook

In conclusion, an enantioselective, Lewis base-catalyzed, intermolecular sulfenoamination has been described. By employing HFIP as the solvent, both anilines and benzylic amines were employed as competent nucleophiles. Of note are anilines bearing functional groups (e.g. BPin) which could serve as a useful handle to further elaborate the core scaffold. A number of olefins, including those bearing heterocycles, were demonstrated. Additionally, electron rich olefins were functionalized in good yields and selectivties demonstrating a robust, stereospecific, thiiranium ion ring opening rather than a reaction proceeding though an open carbocation. Future directions might include the incorporation of more diverse nucleophiles. This might be enabled by finding other protic solvent-sulfenylating agents which can suppress solvent incorporation while allowing for less nucleophilic species (e.g. alcohols or phenols) to be incorporated. Alternatively, the oxysulfenylated product **9** could be isolated and, in a two-step protocol, subjected to catalytic strong acid in the excess of weak nucleophile.

Although the use of milder conditions enabled by HFIP to effect the intermolecular functionalization, the functionalization of these products into useful motifs was key. By employing a β-amido organolithium intermediate, a number of electrophiles were efficiently captured. The corresponding products accessed as a single enantiomer and with exquisite diasteroselectivity. This represents perhaps the most underexplored and promising area to continue this chemistry. Identification and optimization of conditions to access silicon-congaing heterocycles would provide new building blocks for drugs candidates. Additionally, identifying conditions to construct the corresponding carbon heterocycles would also prove useful. Although the scope of electrophiles that can be intercepted serves as an extension, an interesting facet is the solution structure of the β-amido organolithium species clearly which plays a key role in the diastereoselectivity. However, at the time of this writing, no investigations into these lithium dianions (or analogous congeners) have been reported.

Chapter 3. Development of a General Method to Access Enantioenriched 1,2-Amino Alcohols

3.1. Background, Prior State-of-the-Art, Research Objectives

Amino alcohols have served as valuable building blocks in organic synthesis, playing key roles in total synthesis, drug discovery, chiral auxiliaries and asymmetric catalysis.[55] Indeed, the chemistry developed to manipulate the amino alcohol scaffold also engenders their use as valuable precursors to other classes of compounds bearing stereocenters. It would constitute a herculean task to compile the numerous methods described in the literature to access vicinally disubstituted amino alcohols. Given their prevalence in asymmetric catalysis and pharmaceuticals, significant effort is devoted to their construction. As such, what follows is in no way a comprehensive review of the amino alcohol literature, but rather a relevant survey of strategies considered during the outset of this project. As relevant new methods are examined, their histories, scopes and limitations will be discussed.

In general, amino alcohols can be accessed by employing three general strategies: enzymatic, chemo-enzymatic and chemical synthesis (Figure 20A). When constructing libraries where more than milligram quantities of a target are required chemical synthesis is likely the most practical approach. In this regard, constructing the vicinal stereocenters (if applicable) is done in one of two ways. Either the chiral centers can be created synthetically or accessed from chiral pool starting materials. Figure 20B depicts generalized strategies to access 1,2-amino alcohols. This includes functional group manipulations starting from α-functionalized carbonyl species, more modern C-H activation strategies for single heteroatom additions, ring opening of enantioenriched epoxides of aziridines, asymmetric aminohydroxylations as well as various coupling strategies. Typically it is synthetically less demanding to start from chiral pool material and this apparent ease is highlighted in the number of chiral auxiliaries and ligands that are derived from such materials. In this vein, a number of methods to access requisite amino alcohols from the parent amino acids have been developed.

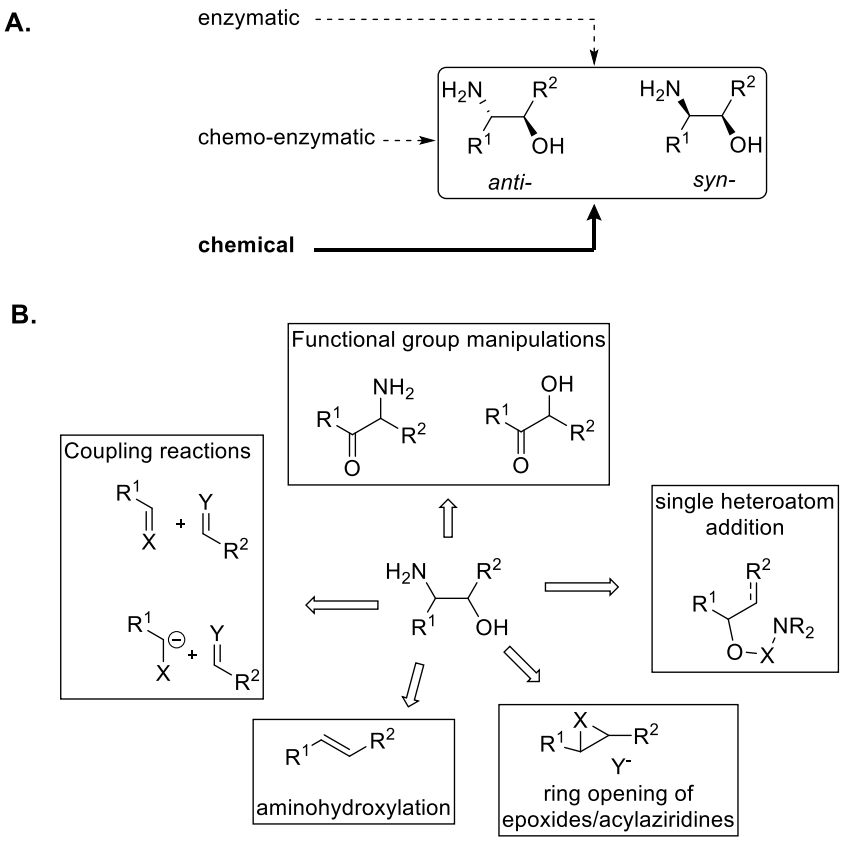


Figure 20. (A) Synthetic approaches to accessing amino alcohols. (B) Chemical retrosynthetic strategies to access 1,2-amino alcohols.

Classically, an amino acid can be directly reduced employing borane, often generated *in situ* from $NaBH_4$ and I_2.[56] Alternatively, strong reducing agents such as lithium aluminum hydride, diisobutylaluminum 19hydride or alane can be used to access the reduced product. If a more mild approach is required a two-step protocol can be employed in which the amino acid is first transformed to the corresponding methyl ester and subsequently reduced. In this case milder reducing agents such as $NaBH_4$ can be used if functional group compatibility is problematic. This strategy will provide either dihydrogen at the C2-position as described above or alternatively, organometallic reagents (e.g. organolithiums, Grignard reagents etc.) can be added to the corresponding amino esters to produce the corresponding C2-disubstituted congeners.

Strategies to access amino alcohols with vicinal stereocenters have also been developed. To this end, α-amino carbonyl compounds undergo diastereoselective addition of hydride or orgnometalic reagents to furnish the corresponding β-amino alcohol (Figure 21).[57] The reduction of α-amino ketones with sodium borohydride proceeds with good facial selectivity at cryogenic

temperatures. The addition of orgnometallic reagents to α-amino aldehydes, while also proceeding with good selectivity, can be challenging. This is in large part to the tendency for these starting materials to racemize under the reaction conditions.

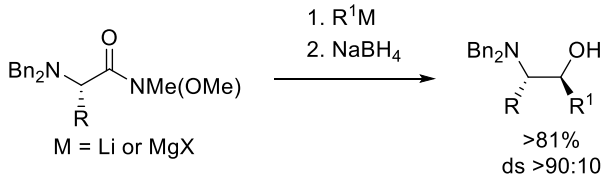


Figure 21. Sequential addition of organometallic nucleophiles and diastereoselective reduction to afford 1,2-amino alcohols.

Vicinal 1,2-amino alcohols with adjacent stereocenters can also be accessed through the setereoselective opening of enantioenriched epoxides (Figure 22, entry 1). The requisite epoxides can be accessed through a number of methods including the Sharpless asymmetric epoxidation, Shi epoxidation and Jacobsen epoxidation. While the latter two provide access epoxides without the aid of a directing group, the Sharpless asymmetric epoxidation requires the presence of an allylic alcohol somewhat limiting its utility in this regard. An issue that arises when opening epoxides is regioselectivity. This problem can be overcome though either choice of substrate (i.e. having a benzylic position to direct opening) or judicious choice of reagent. While soluble azide source such as trimethylsilyl azide generally provide oxirane opening at the least sterically hindered position, employing tributyltin azide or diethylamluminum amides has been shown to change the regioselectivity of this opening.[58,59] An analogous and viable alternative to the stereospecific, nucleophilic opening of epoxides is the ring opening of cyclic sulfates by nitrogen nucleophiles (Figure 22, entry 2).[60] Cyclic sulfates can be accessed via the corresponding 1,2-diols which are readily accessed via the Sharpless asymmetric dihydroxylation.

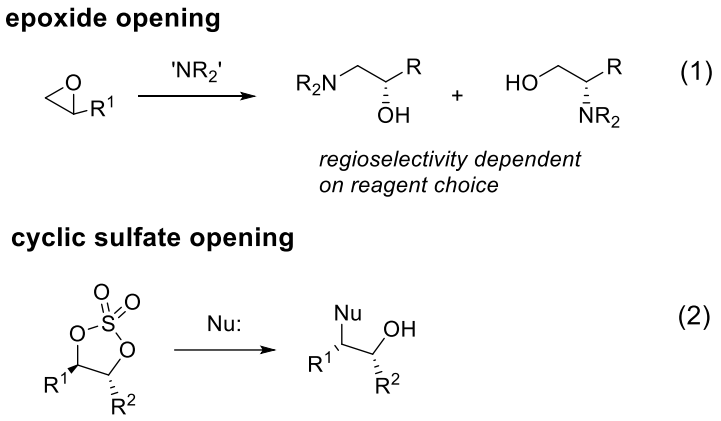


Figure 22. (A) Regioselective epoxide ring opening. (B) Nuclophilic ring opening of cyclic sulfates.

Another reliable method to access these motifs is through the Henry reaction (Figure 23).[61] Unlike the previously described methods which relied on forging a bond between a peripheral group, the Henry reaction forges the central C-C bond. The immediate product of this transformation is the β-nitro alcohol which can be readily reduced to the corresponding amino alcohol. A number of asymmetric versions of this method have been developed in employing ligands ranging from Binol salts to Copper(II) salts of bisoxazolines. While this initially seems an attractive method to rapidly access amino alcohols, the Henry reaction has some challenges associated. Often, the β-nitro alcohol product can be unstable and undergo dehydration – especially when employing an aryl aldehyde precursor. Additionally when employing sterically hindered carbonyl compounds, a base-catalyzed, self-condensation may occur preferentially.

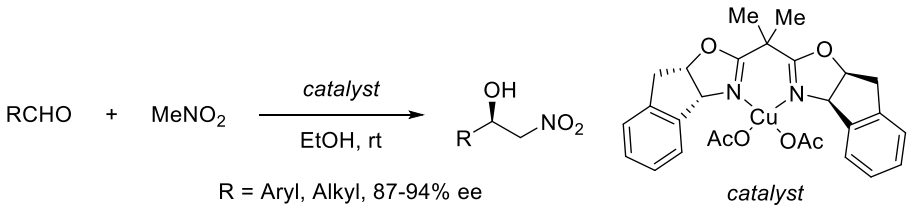


Figure 23. Copper-catalyzed, enantioselective Henry reaction.

As mentioned previously, one key role of amino alcohols is in asymmetric catalysis. Serving as ligands themselves, or as valuable precursors, amino alcohols are indispensable tools for any practicing synthetic organic chemist. In conjunction with a machine learning, informatics based platform the Denmark laboratories undertook a synthetic effort to access 40 diverse and

novel bisoxazolines. The central hypothesis behind this undertaking is that the majority or bisoxazolines, and ligands in general, employed in asymmetric transformations lack chemical diversity. As a result of this lack of diversity, a number of asymmetric transformations are unable to be optimized to achieve synthetically useful selectivity. The following brief discussion gives a brief overview of how the partnership between asymmetric catalysis and machine learning, known as cheminformatics, operated when this synthetic effort was initially undertaken.

A novel workflow to optimize method development was employed to marry the evaluation of ligands with a machine learning algorithm to rapidly identify a more selective ligand. Figure 24 briefly summarizes the envisioned workflow to determine an optimal ligand design. For a given ligand scaffold (e.g. bisoxazolines) all possible compound permutations are built *in silico*. Then 3D-descriptors are calculated to characterize their steric and electronic properties. From these descriptors, a Kennard-Stone algorithm is applied to the *in silico* library to select a subset of compounds that represent the chemical space covered by the library. These selected ligands comprise the "training set" and are the ligands that are selected for synthesis and tested in an asymmetric transformation. By systematically diversifying the training set the potential of obtaining a selective catalyst in the first round of optimization is increased and provides a platform for predictive model development. After determining the desired training set, the selected ligands are synthesized and evaluated for their performance in a particular reaction. It is important to note that this training set is universal and can be used for any reaction. The remainder of the discussion will center on our prolonged efforts to access this training set and a search for a revised approach.

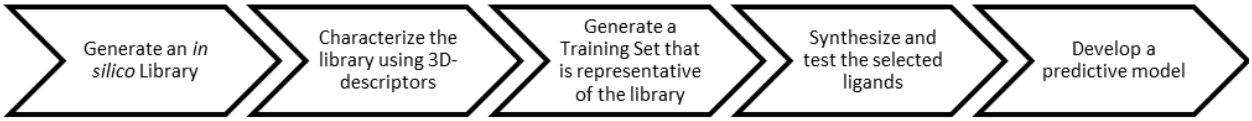


Figure 24. Outline of Cheminformatics approach to reaction optimization.

Although both computational and synthetic efforts existed simultaneously, this chapter covers the challenges in identifying appropriate synthetic methods to access large libraries of enantioenriched, β-amino alcohols. Approaches and synthetic efforts will be discussed as they occurred chronologically as to not minimize the challenges associated with creating diverse libraries of what appears to be a ubiquitous motif. Additionally, for the sake of full disclosure, it

should be noted that initial approaches to access the first bisoxazoline training set were in place prior to my joining the project and not my own intellectual contribution; however, for clarity they are presented here. The subsequent sections detail a collaborative evaluation of methods to access large quantities of diverse amino alcohols. These include efforts towards: enantiospecific cross coupling, samarium iodode mediated reductive cross coupling and diasteroselective, 1,2-additon to imines derived from Ellman sulfinamides. The criteria that define an ideal method are highlighted and problematic limitations discussed.

3.2. Initial Strategies for Stereoselective 1,2-Amino Alcohol Synthesis

The general disconnections to access C2-symmetric bisoxazolines are shown in Figure 25. Most bisoxazolines are accessed by the corresponding enantioenriched, 1,2-amino alcohol and a diacid bearing the requisite substituents at the bridging position. Amino alcohols can be accessed in a number of ways, including those described above; however, the general approach taken in the synthesis of the first generation training set was to first access the corresponding amino acid.

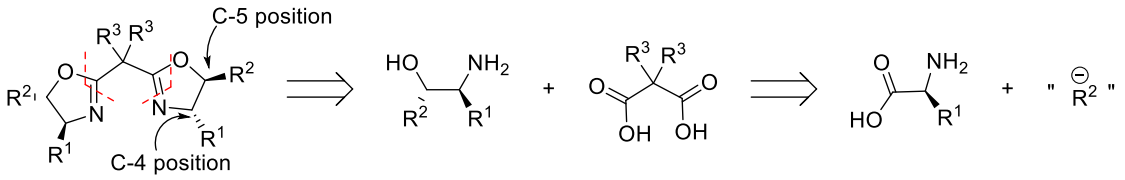


Figure 25. Retrosynthetic analysis of bisoxazoline ligands.

The training set could be efficiently broken down into four groups with respect to the substituent pattern of the final bisoxazoline (Figure 26). Those bearing aryl substituents at the 4-position were derived from the asymmetric Strecker reaction (Figure 26, entry 1).[62] Those bearing benzyl-substituents at the 4-position would be derived from the asymmetric O'Donnell alkylation reaction (Figure 26, entry 2). In the preceding two cases, the identity of the substituents at the 5-position of the bisoxazoline was irrelevant as installation of these substituents would occur later. Finally, bisoxazolines derived from symmetric stilbenes or styrenes would be accessed by Sharpless asymmetric dihydroxylations and subsequent functional group interconversions (Figure 26, entries 3 and 4)

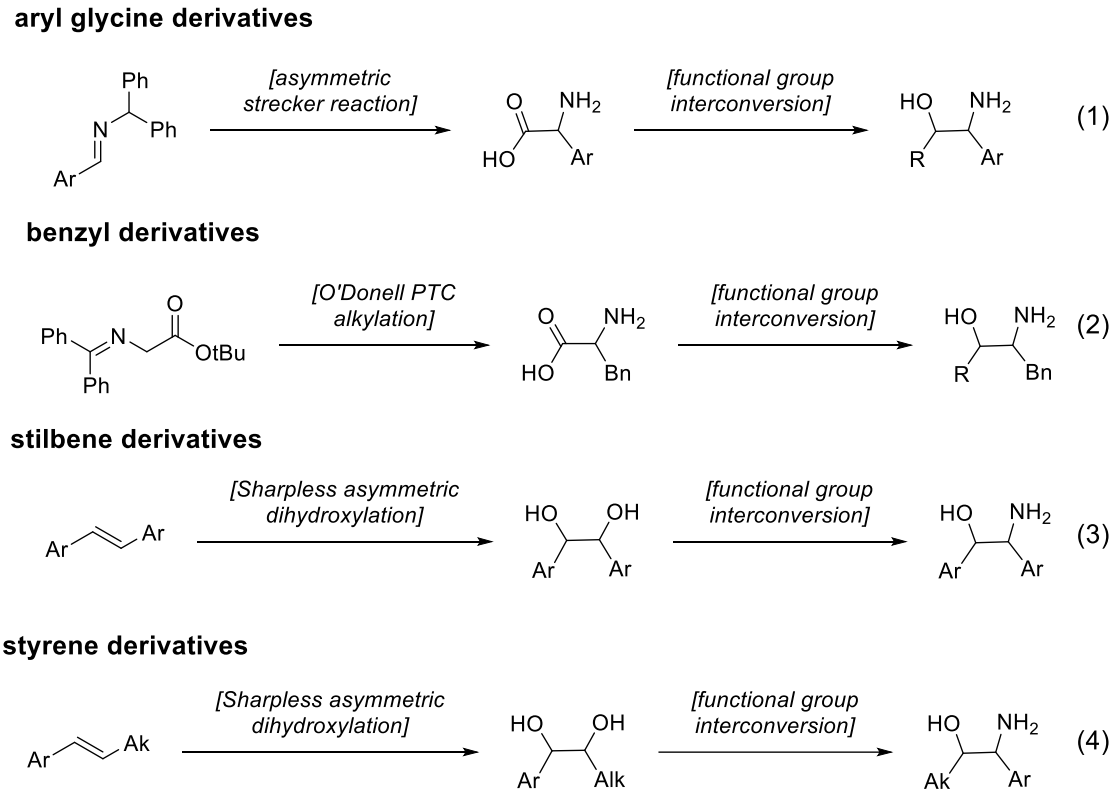
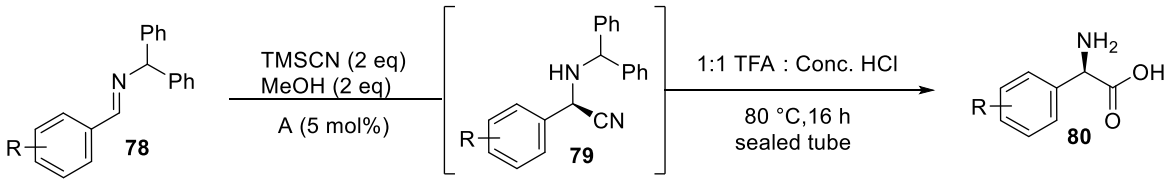


Figure 26. Synthetic strategies to access 1,2-amino alcohols for the first generation bisoxazoline training set.

In the forward direction, generic imine **78** is treated with TMSCN and methanol under the actions of Jacobsen's catalyst to afford cyanohydrin intermediate **79**. Intermediate **79** is then treated in a sealed tube with 1:1 trifluoroacetic acid/HCl to afford the requisite amino acid **80** in good yield and moderate to good enantioselectivity (Scheme 5).

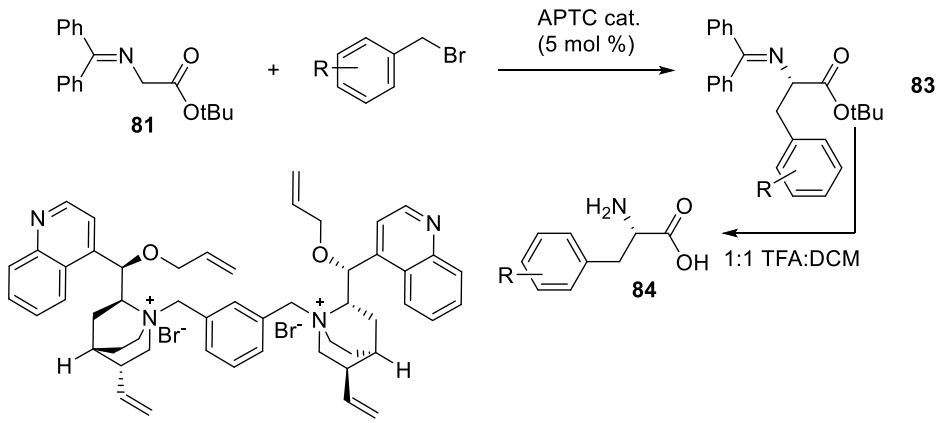
Scheme 5. Preparation of amino acids by the asymmetric strecker reaction.



Bisoxazolines bearing benzyl substituents could readily be traced back to amino acids derived from the O'Donnell asymmetric phase transfer alkylation (Scheme 6).[63] Generic imine **81** is treated under phase transfer conditions with the corresponding benzyl halide and catalyst **82**

to give the mono-alkylated product **83**. Global deprotection returns the desired amino acid **84** in excellent yield and enenantioselectivity.

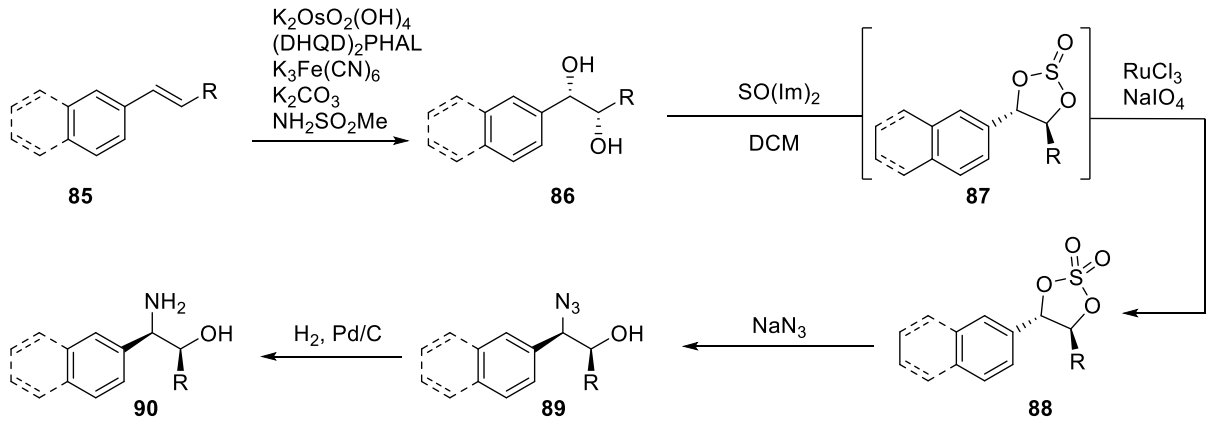
Scheme 6. Synthetic route to benzyl containing amino acids.



APTC cat. **82**

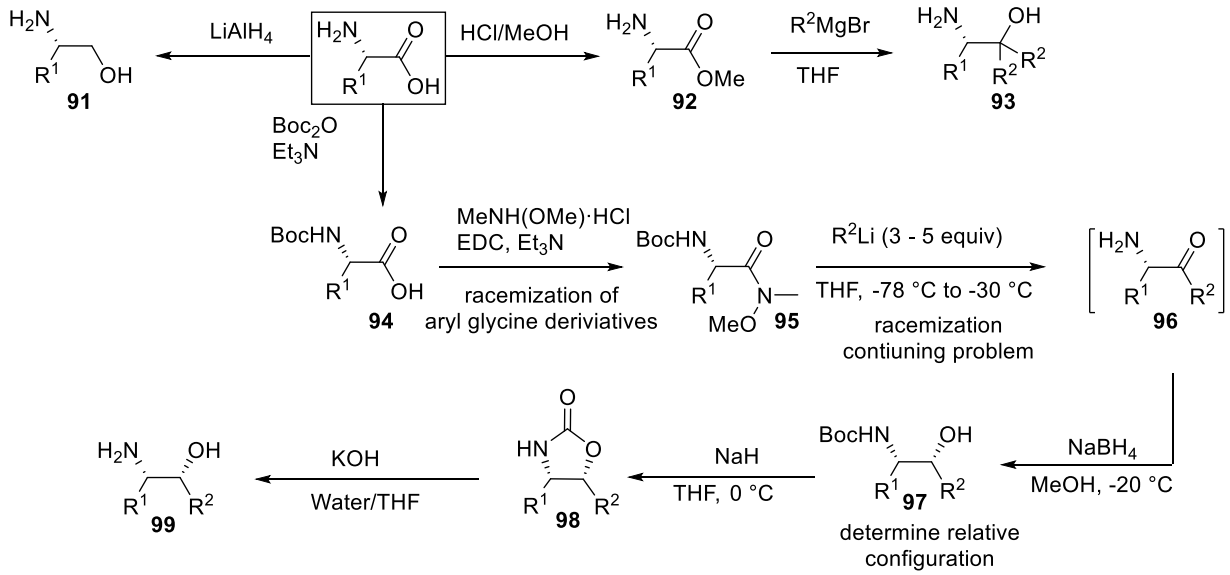
The final two groups of bisoxazolines, which contain *identical* aryl substituents on both the 4- and 5-position, or an aryl subsitutent in the 4-position and an alkyl in the 5-position were did not require accessing the corresponding amino acid. In the forward direction, generalized in Scheme 7, starting olefin **85** is subjected to standard dihydroxylation conditions. Depending on the identity of the substituents these reactions took anywhere from 1 day when substituents were small and up to 7 days with larger substituents (e.g *t*-Bu). Following dihydroxylation, intermediate **86** was treated with sulfoniyldiimixazole to form the cyclic sulfite **87** which was immediately oxidized to the cyclic sulfate **88**. Diastereospecific ring opening with sodium azide afforded the β-azido alcohol **89** generally in good yield with complete preservation of enantioselectivity. Reduction of the azide afforded the requisite amino alcohol **90**, again in good yield. Taken together, three robust chemical transformations provided access to the chemical diversity required at the 4-position.

Scheme 7. General approach to first generation training set amino alcohols.



Critical to the universal training set was accessing bisoxazolines bearing not only diversity at the 4-position, but at the 5-position as well. This aspect was deemed necessary as subtle changes in the geometry surrounding the reaction center might influence the selectivity or a particular transformation. While bisoxazolines derived from the Sharpless dihydroxylation have the stereocenter at the 5-position installed, those derived from amino acids require more synthetic effort. The strategies employed to functionalize this position are summarized in Scheme 8. There were three classes of amino alcohols that needed to be synthesized from the corresponding amino acids: (1) those bearing dihydrogen at the 2-position, (2) amino alcohols with disubstitution at the 2-position, and (3) amino alcohols bearing stereocenteres at both carbons.

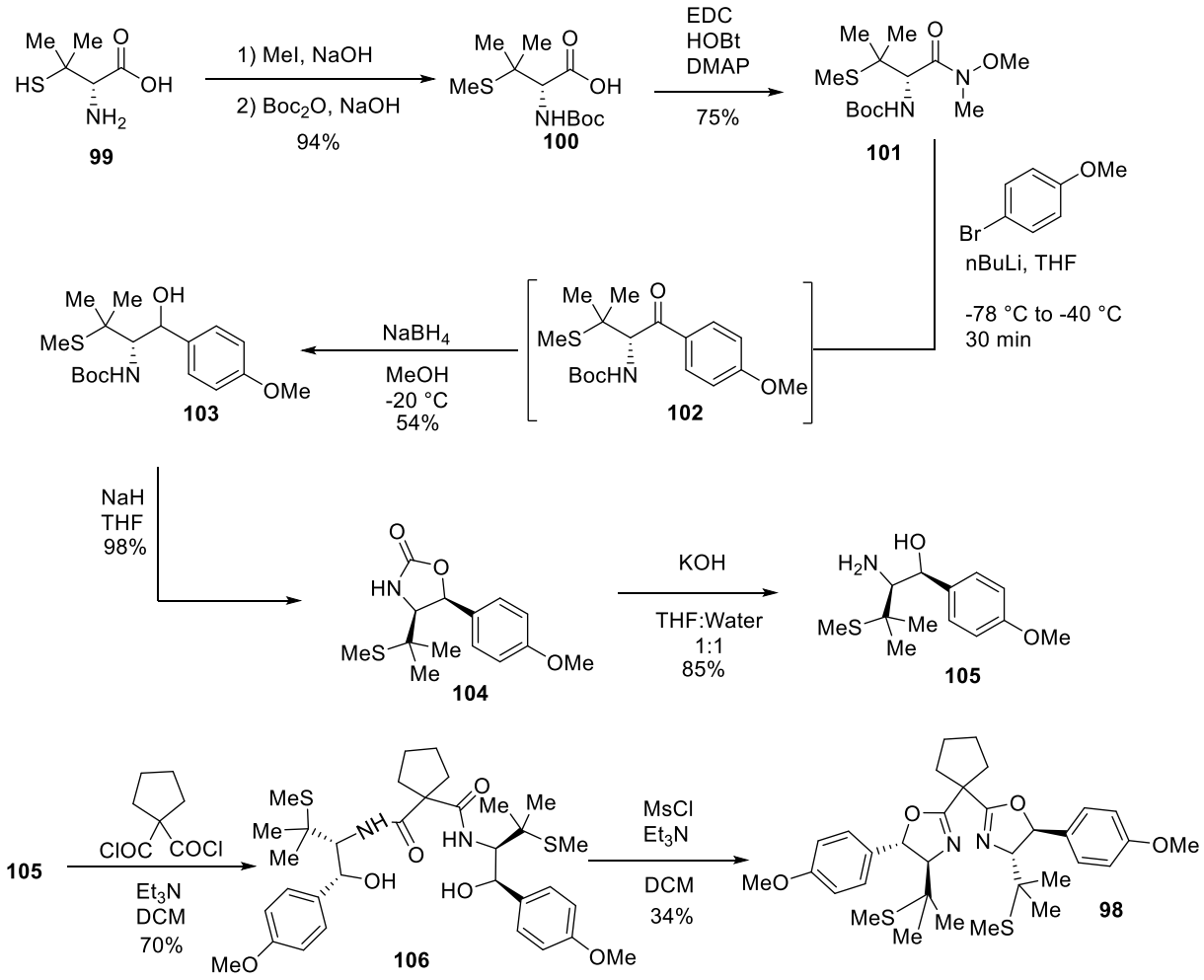
Scheme 8. First generation approaches to amino acid functionalization.



Access to amino alcohols bearing dihydrogen at the 2-position was readily accomplished under the action of lithium aluminum hydride. These transformations are well known and gave reliable results. In a similar vein, disubstituion at the 2-position was easily accomplished in a two-step protocol. First, esterification of the amino acid provided methyl ester **92** in good yield. Subsequent double addition of either aryl- or alkylmagnesium bromide cleanly provides the disubstituted amino alcohol **93** to be carried forward. Serious problems arose when attempting to access vicinally disubstituted β-amino alcohols from the parent amino acids. This sequence began with Boc-protection of the requisite amino acid to afford **94**, generally in good yield. Weinreb amide formation of **95** employing EDC worked well; however, in some aryl glycine derivatives partial racemization of the product was seen. Treatment of **95** with alkyl or aryl lithium nucleophile to provide α-amino ketone **96** was plagued with problems of racemization in the presence of the Brønstead basic nucleophile. Diastereoselective reduction employing sodium borohydride imparted some much needed stability to the product. Treatment of **96** with sodium hydride afforded oxazolidinone **97** which was needed to determine the relative configuration after reduction by ^{1}H NMR spectroscopy. Finally, ring opening employing KOH gave the requisite amino alcohol. Overall, this sequence required six synthetic manipulations after obtaining the requisite amino acid.

Additionally, during the course of this effort, it was found that accessing each of the 40 desired target bisoxazolines required individual optimization. For example, the following optimization was required to access penicillamine derived bisozazoline **98** (Scheme 9). Starting from commercially available penicilamine **99**, methylation followed by protection with Boc anhydride afforded **100** in good yield. Weinreb amide formation under classic peptide coupling conditions provided access to **101**. Initial attempts to access α-amino ketone **102** were met with limited success. Treatment of **101** with 4-methoxyphenyl lithium at -78 °C provided only 10% conversion to the desired product **102** in 1.5 hours. Raising the temperature to -50 °C increased conversion to 20% in 30 minutes. Finally, increasing the reaction temperature to -40 °C provided complete conversion in under 30 minutes. Subsequently, **102** containing a labile stereocenter, was taken forward without purification and subjected to diastereoselective reduction to afford **103** which proceeded well. Attempts to directly form amino alcohol **105** with HCl/methanol were unsuccessful, resulting instead in epimerization of the benzylic alcohol. To circumvent this problem, and establish relative configuration, oxizolidinone **104** was formed by treatment with sodium hydride followed by ring opening under basic conditions for provide **105**. Bisamide **106** was accessed through the corresponding bis-acid chloride in good yield. Invertive closure afforded the corresponding bisoxazoline **98** in low yield, with a significant portion of the material failing to undergo complete cyclization. As is evident, developing a large and diverse library through these multi-step synthetic routes is not viable and ill-advised. Given the synthetic effort required for each ligand and the optimization required for each step, an alternative strategy had to be developed for this project to move forward.

Scheme 9. Synthetic route to penicilamine-derived bisoxazoline.



In total, 28 bisoxazolines were accessed during this effort – in large part owing to the efforts of the entire Denmark laboratory – and were used to examine an asymmetric aziridination. Ultimately, a superior ligand was not found despite these efforts, for which there were likely two principle causes. One, owing to the synthetic challenges, numerous concessions and modifications had to be made to the training set thereby altering the chemical space that was being evaluated. Second, the computational descriptors failed to accurately represent chemical space and therefor the training set did not capture the necessary steric and electronic perturbations to the ligands.

3.3. Evaluation of Reported Methods and Alternative Strategies

Initial strategies focused on the diastereoselective installation of a stable, secondary tin species which could undergo enantiospecific cross coupling to furnish a library of amino alcohol precursors. This strategy was largely inspired by the work of Biscoe and coworkers who reported an enantiospecific Stille cross-coupling of alkylstannanes by employing alkylazastannatranes.[64,65] The use of alkylazatannatranes is critical to the success of this transformation as they have been shown to selectively transfer alkyl groups. This phenomenon is a result of the intramolecular coordination between tin and nitrogen which activates the alkyl group to undergo transmetallation. It was anticipated that by employing this strategy, a common, tin-containing, intermediate could readily be diversified into a library of amino alcohol precursors. Although this strategy would not cover all the requisite substitution patterns (e.g alkyl, benzyl) it was anticipated that other methods, such as the O'Donnell PTC reaction, would be able to fill in those gaps. Furthermore, this strategy fulfilled a critical criterion in large building large libraries of compounds – work from a common, late stage intermediate. This dimension was missing from initial approaches.

To access the putative organotin intermediate **107** three distinct strategies were envisioned: (1) the organotin species would be installed through nucleophilic addition into an imine species, (2) directed lithiation would provide the requisite secondary alkyl anion to intercept an electrophilic tin, or (3) a radical decaboxylation would furnish a secondary radical which could subsequently undergo recombination with a tin radical (Figure 27).

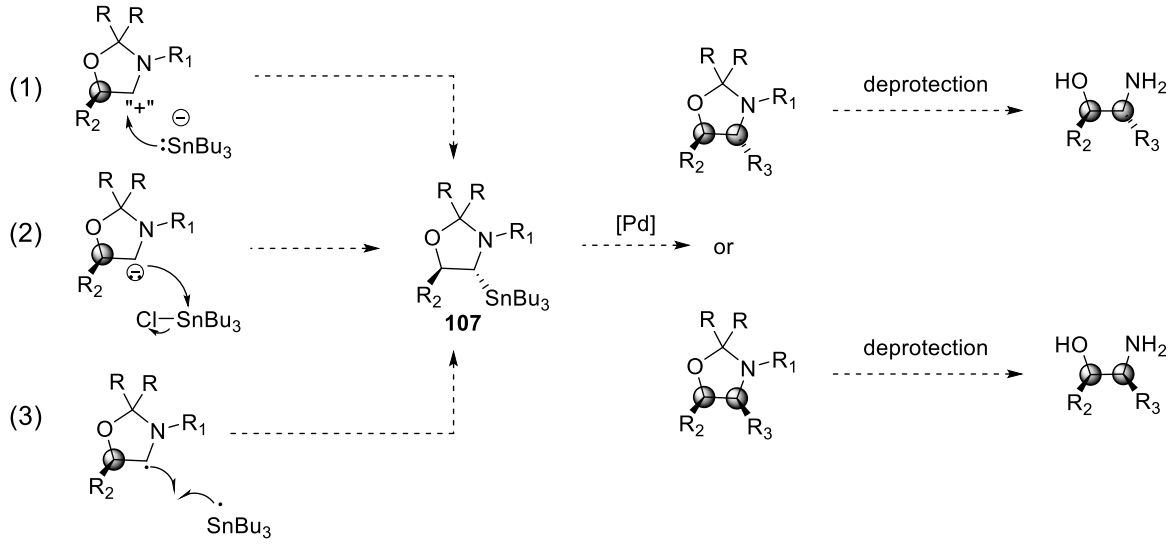
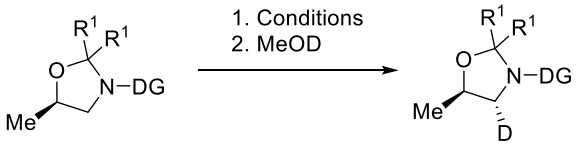


Figure 27. Approach to tin-containing, amino alcohol precursor.

Installation of the organotin unit by directed lithiation was first attempted on N-Boc oxazolidinone **108** (R^1 = OH). Treatment with *s*-BuLi in THF at -78 C (Table 3, entry 1) resulted in complete decomposition of the starting material (after quench with MeOD). Examining the effects of solvent (Et_2O) and additives (TMEDA) afforded no change in the outcome. Lowering the temperature to -100 °C also afforded decomposed product as did employing *t*-BuLi. Hemiaminal **109** (R^1 = Me) was constructed, a substrate that more closely resembles substrates for which this chemistry has successfully been employed. Subjecting N-Boc protected hemiaminal to similar conditions resulted in decomposition of the starting material (entries 5 and 6). Changing the protecting group to pivaloate (compound **110**) resulted in the complete loss of reactivity even when employing *t*-BuLi. The decomposition of **109** was more than likely the result of successful deprotonation followed by rapid β-elimination. Failure to effect deprotonation of **110** came from the inability of the sterically encumbered pivaloate to adopt the requisite conformation to direct the deprotonation. In any event, this approach to installing tin was quickly abandoned.

Table 3. Directed metalation reaction optimization.

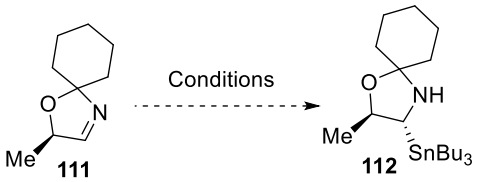
108 (R^1=OH, DG = Boc)
109 (R^1=Me, DG = Boc)
110 (R^1=Me, DG = Piv)



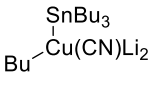
entry	R^1	DG	base	solvent	temp, °C	Result
1	OH	Boc	*s*-BuLi	THF	-78	Decomp.
2	OH	Boc	*s*-BuLi	Et_2O	-78	Decomp.
3	OH	Boc	*t*-BuLi	THF	-78	Decomp.
4	OH	Boc	*s*-BuLi	THF/Et_2O	-100	Decomp.
5	Me	Boc	*s*-BuLi	THF	-78	Decomp.
6	Me	Boc	*s*-BuLi	Et_2O	-78	Decomp.
7	Me	Piv	*s*-BuLi	Et_2O	-78	n.r.
8	Me	Piv	*t*-BuLi	Et_2O	-78	n.r.
9	Me	Piv	*t*-BuLi	Et_2O	-20	n.r.

Seeking to employ an alternative strategy, imine **111** was synthesized in three short synthetic steps.[66] The requisite hemiaminal derived from commercially available L-alanine was oxidized to the corresponding imine formed via *in situ* generated chloramine followed by elimination to furnish **111**. A number of conditions were evaluated, summarized in Table 4, in an attempt to form **112**. Unfortunately, no desired product was observed. This comes likely as a result of the diminished electrophilicity of the imine.

Table 4. Addition of tributyltin nucleophiles to **111**.



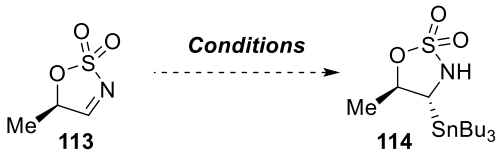
entry	nucleophile	solvent	temp, °C	time, h	Result
1	Bu_3SnLi	THF	-40	1	Decomp.
2	Bu_3SnTMS	THF	-60	1	Decomp.
3	Bu_3SnLi	THF	-78	1	Decomp.
4	A	THF	-78	2	Trace



A

Taking inspiration from Chong and coworkers, imine **113** was synthesized and incorporates the electron withdrawing sulfonamine to more closely resemble previous reports.[67] When imine **113** was subjected to the reaction conditions outlined in Table 5 there was complete consumption of starting material albeit unproductively. Effects of temperature on the reaction were examined as well as capturing the resultant nitrogen anion intermediate with a competent electrophile however these strategies were unsuccessful. Cryogenic quench with methanol and subsequent buffered workup still resulted in no observed product. Ultimately it was deemed that the instability of the resulting product or key intermediates to reaction conditions was not amiable to our pressing need to create a rapidly diversifiable library.

Table 5. Addition of tributyltin nucleophiles to **113.**



entry	nucleophile	additive	solvent	temp, °C	time, h	Result
1	Bu_3SnLi	-	THF	-78	1	Decomp.
2	Bu_3SnTMS	$LiClO_4$	MeCN	25	18	Decomp.
3	Bu_3SnLi	-	THF	-78	1	Decomp.
4	Bu_3SnLi	-	Et_2O	-78	1	Decomp.

Given the challenges associated with the functionalization-cross coupling approach, a reevaluation of the literature was warranted. It was important to identify methods that not only would be amenable to rapidly building large libraries of amino alcohols (which in turn could be used in a number of ligand classes) but to evaluate methods that were known to give excellent diastereoselectivity. Although employing chiral auxiliaries was initially rejected, presumably owing to poor atom and step economy, numerous methods with demonstrated broad scope and good selectivity exist which employ chiral auxiliaries. Ultimately, it was critical to develop a general method to access a large library of amino alcohols no matter the cost.

One method that stood out was a SmI_2-mediated pinacol-type coupling between *N*-*tert*-butanesulfinyl imines and either imines, aldehydes or ketones (Figure 28).[68] Indeed, this strategy has been employed in a number of synthetic methods and total synthesis to access the corresponding diamine or amino alcohol. Two critical features stood out about this class of transformation: (1) in general, products are obtained in excellent diastereoselectivity and good yields and (2) the resulting products were deprotected to provide the corresponding diamines or amino alcohols in high enantioslectivity and yield. One potential drawback was the cost of SmI_2 given that each of the requisite amino alcohols would need to be made on gram scale; however, methods are described to produce SmI_2 and lower the commercial cost. [69]

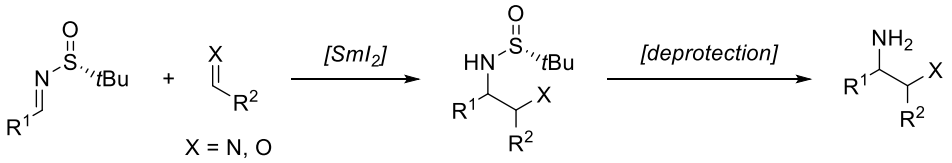


Figure 28. SmI_2 mediated cross coupling of sulfimines and imines or aldehydes

In particular, two related reports stood out which provided evidence that a pinacol-type coupling strategy might prove to be useful. The first by Xu in 2004 described the SmI_2-mediated cross couplings of *N*-*tert*-butansulfinyl imines with nitrones (Figure 29).[70] While not directly applicable, the reported diastereoselctivies and yields were promising. More importantly, a modest scope was presented which showed a number of aromatic *N*-*tert*-butansulfinyl imines coupling efficiently with aliphatic nitrones. Furthermore, an efficient deproptection protocol was described which buoyed confidence that this might prove to be an efficient method to access large libraries of derivatives. A putative mechanism was proposed wherein the nitrone is reduced

with two equivalents of SmI_2 to the α-aza-nucleophile. Following reduction, an intermolecular addition of the *N*-*tert*-butanesulfinyl imine provides the corresponding product.

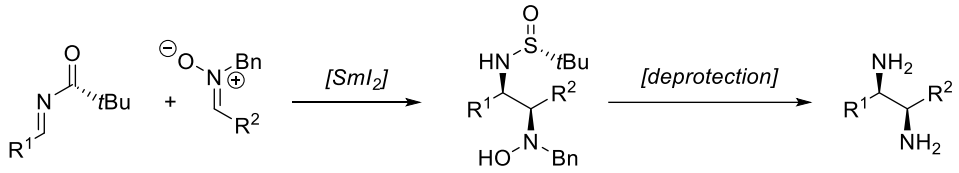


Figure 29. SmI_2 mediated cross coupling of sulfimines and nitrones.

A second report in 2005 by the same group describes an extension of this method to access β-amino alcohols from the corresponding aldehydes and ketones.[71] Again employing SmI_2 as a reducing agent and *t*-BuOH as a proton source both aromatic and aliphatic *N*-*tert*-butanesulfinyl imines were coupled with aliphatic aldehydes in excellent yields and diastereoselectivites. A broad substrate scope was demonstrated wherein electron neutral, rich and deficient aryl *N*-*tert*-butanesulfinyl imines were readily coupled with a number of linear and α-branched alphatic aldehydes. With few exceptions, all products were obtained in greater that 99:1 d.r. and greater than 80% yield. Furthermore, multiple methods for cleaving the sulfinyl group were demonstrated with no loss in enantioselectivity. Overall, this method represented a promising approach to rapidly access the library of amino alcohols that were necessary for a cheminformatics approach to ligand optimization.

While the efficacy and diastereoselectivity of this transformation had excellent precedent, a thorough evaluation of the scope of this transformation was lacking. Specifically, only simple arenes had been previously examined whereas more complex systems were still unknown. Specifically, the competency of polyaromatics and heterocycles was unknown, as was the diasteroselectivity when the substituent of the aldehyde was not aryl or methyl. Ultimately, it was found that when employing isobutyraldehyde and (*R*,*E*)-*N*-(4-methoxybenzylidene)-2-methylpropane-2-sulfinamide provided product **116** in 75% yield (NMR) and 95:5 d.r. Extending this to electron deficient sulfonimines, product **117** was obtained in a significantly lower yield but comparable d.r. Similar results were obtained when employing 2-substitued napthylimine to provide **118**. Ultimately, when this method was examined against more "exotic" substrates severe limitations were discovered. Product **119** containing a 4-pyridine was obtained in 43% yield with a dismal 56:44 d.r. Thiophene, chosen to represent π-electron rich arenes, gave good diastereoselectivity but yield suffered. This continued when examining extended polyaromatics

120 and **121**. This unfortunate lack of scope is insufficient to provide the library necessary to enable a cheminformatics of bisoxazolines and thus a new transformation needed to be found.

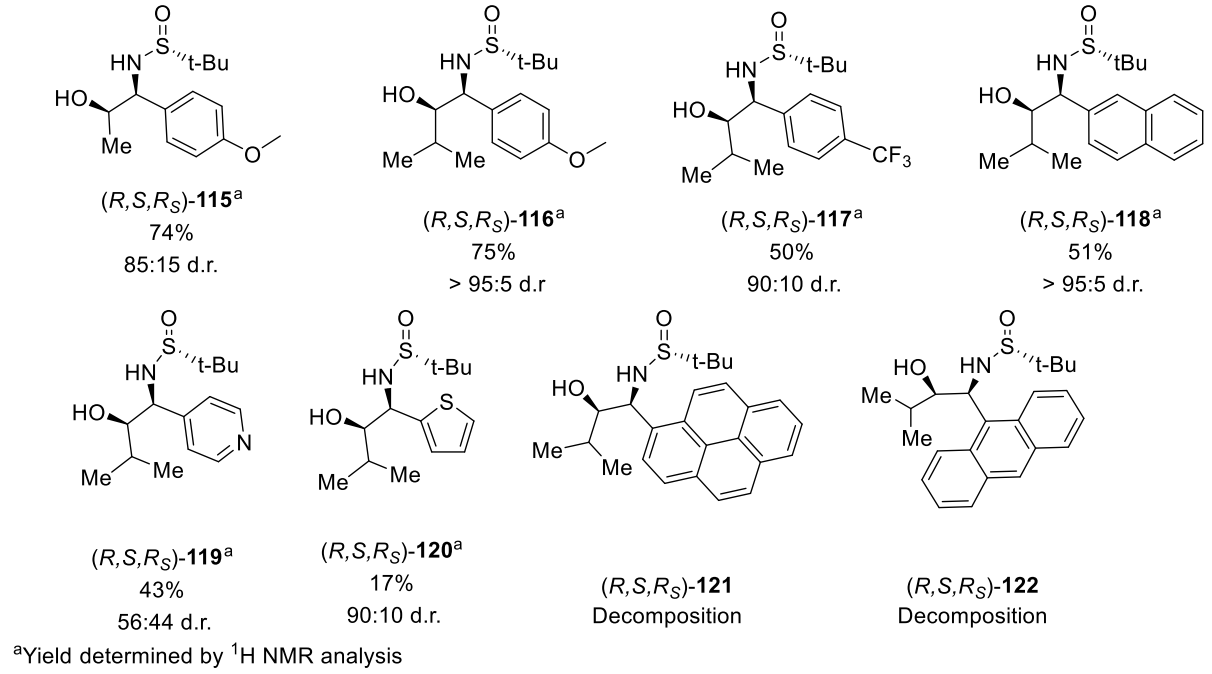


Figure 30. Evaluation of SmI_2 mediated cross coupling reaction scope.

3.4. 1,2-Disubstituted β-Amino Alcohols via Addition to *N-tert*- Butylsulfinimines

3.4.1. Background and Prior State-of-the-Art

Inspired by the excellent diastereoselctivity of the SmI_2-mediated cross pinacol couplings, as well as the relative ease with which sulfinamines can be removed, a reevaluation of the approach to access this large library of amino alcohols was warranted. Indeed a number of valuable lessons had been learned during the course of this investigation. Ultimately, four criteria were enumerated that needed to be met for a viable approach to access large libraries of amino alcohols: (1) the approach should be highly diversifiable, ideally at a late stage intermediate. (2) It was critical to avoid erosion of stereochemical purity during the course of the synthetic sequence. This point was of particular importance reflecting on lessons learned in previous approaches where separating *d,l* and *meso* bisoxazolines proved tedious. (3) Simple, inexpensive starting materials would be best as the amino alcohols would need to be produced on gram scale. Finally, (4) the process needed to be robust and scalable as it was unknown exactly what amino alcohols would need to be made or who would be making them. It was believed that the 1,2-

additon of orgnometallic nucleophiles to protected alkoxy sulfinyl imines would satisfy the above criteria.[72]

Two concurrent reports by Ellman and Barrow disclose the diastereoselctive addition of Grignard reagents to α-siloxy sulfinimines (Figure 31).[73,74] Both describe the development and optimization of the 1,2-addition of various Grignard reagents afford, after global deprotection, the corresponding β-amino alcohols. In all cases addition of Grignard reagents provide the corresponding products in excellent yields and diastereoselectivies. By employing non-coordinating solvents (e.g. toluene, CH_2Cl_2) a number of aryl and alkyl Grignard nucleophiles are incorporated. Additionally, the effect of the α-hydroxy protecting group was examined. It was found that the identity of the protecting group bore little effect on the diastereoselectivity; however, employing trimethylaluminium as an additive significantly improves the diastereoselectivity in some cases.

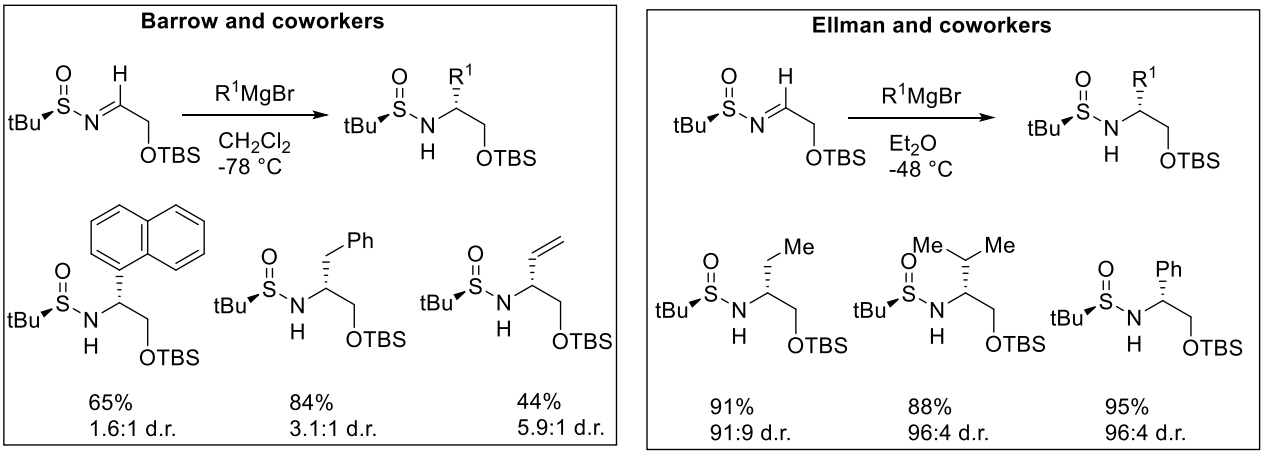


Figure 31. Diastereoselective 1,2-conjugate addition of Grignard reagents to sulfonimines.

The authors postulated that the excellent diastereoselectivity is a result not only of control from the sulfinyl group but rather from metal chelation to the alkoxy group (Figure 32). This hypothesis is corroborated by a change in the sense of induction of the corresponding products from when the corresponding sulfinyl aldimines are employed. It is presumed that this coordination proceeds through a chair-like transition state wherein the pendant alkoxy motif coordinates to the organometallic and overrides the inherent diastereoselectivty.

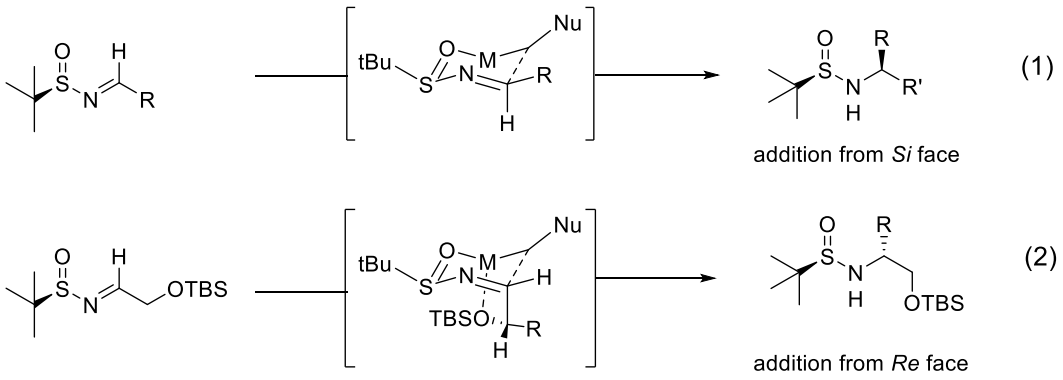


Figure 32. Putative transition states with influence of pendant alkoxy group.

A follow up report by Ellman expanded on the scope of this transformation by elaborating the scope to include *N*-*tert*-butanesulfinyl (*R*)-alkoxy aldimine starting materials.[75] Crucially, it was found that these starting materials could be prepared from the corresponding lactals without epimierization of the α-stereocenter. A small library of aryl and alkyl Grignard reagents give access to the corresponding 1,2-addition products in good yields and with good diastereoselectivities. Unlike previous reports, the identity of the protecting group played a role in determining if a *syn* or *anti*-1,2-amino alcohol is obtained. When TBS is used, the *anti*-isomer is obtained in good yield and excellent diastereoselctivity whereas when employing TBDPS generally provides the *syn* isomer in modest selectivity (Figure 33). Curiously, this trend does not hold in all cases however no causative explanation is given. Taken together, these three reports proved a promising lead in identifying a method to access the required amino alcohols.

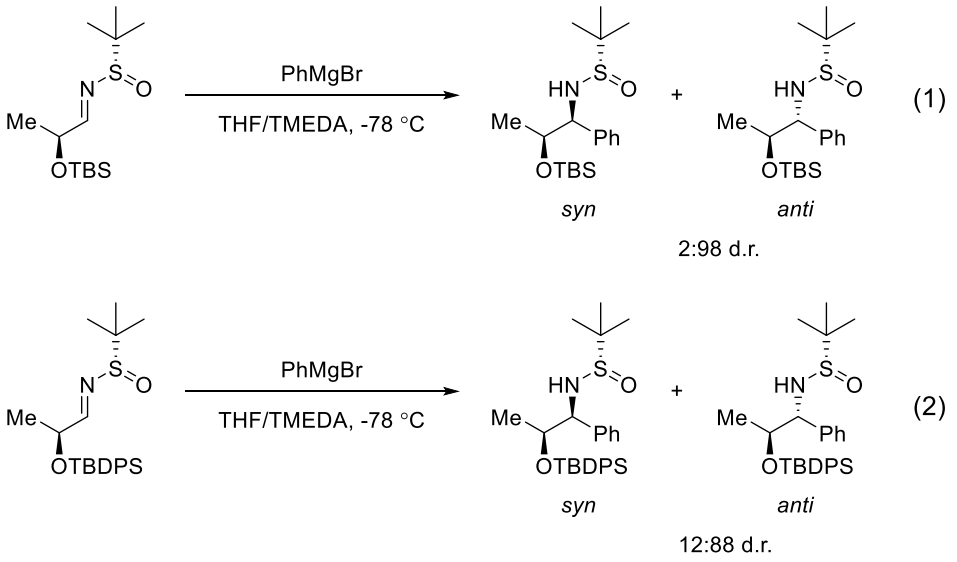


Figure 33. Influence of protecting group identity of diastereoselectivity.

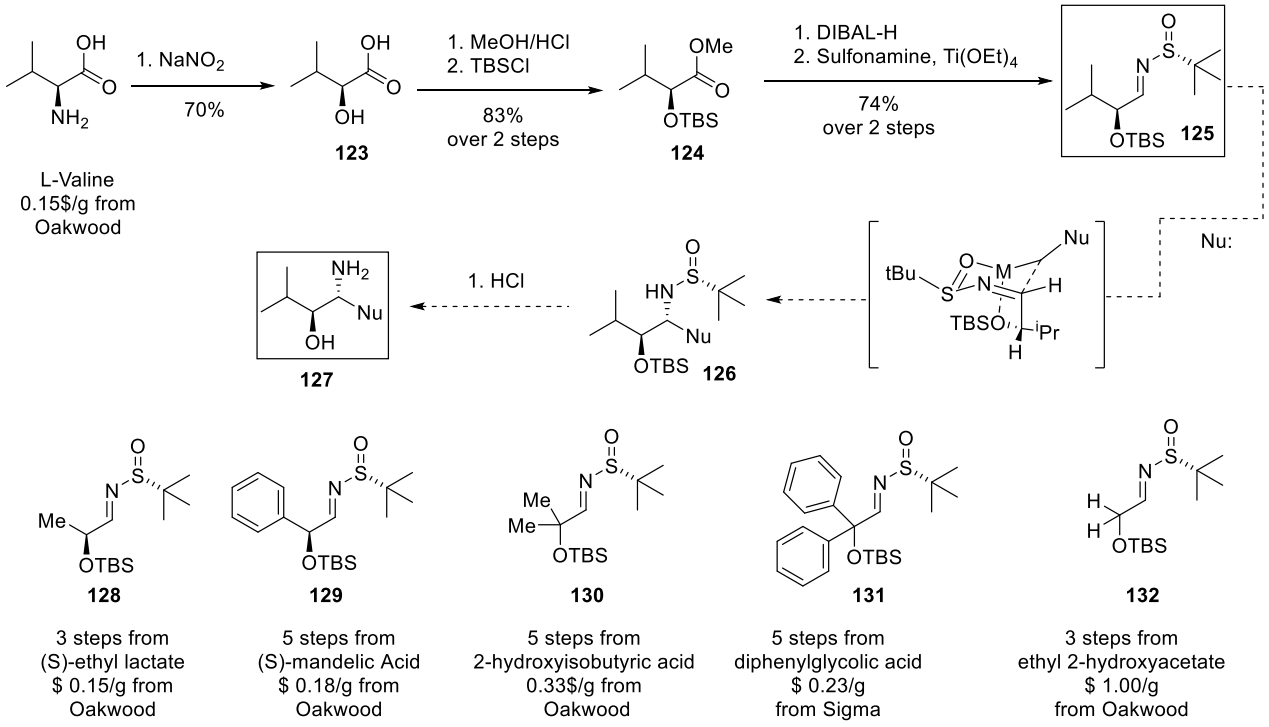
3.4.2. Development and Scope

Synthesis of the α-siloxy sulfinimine common intermediates began with commercially available amino acids or enantioenriched α-hydroxy esters. A representative reaction sequence starting from L-valine is shown in Scheme 10. Treatment of L-valine with sodium nitrite in water provides the stereretentive hydroxylation via anchimeric assistance from the pendant carboxylic acid to afford **123**. Sequential methyl ester formation and protection provides α-siloxy methyl ester **124**. DIBAL-H reduction to the corresponding aldehyde and condensation of commercially available (*R*)-tert-butylsulfinamine returns the requisite imine **125** with no loss of stereochemical purity. This common intermediate, obtained in five facile and high yielding steps, is the key intermediate needed to build the required library of 1,2-amino alcohols. Addition of the requisite organometallic nucleophile provides the amino alcohol precursor **126**. Finally, global deprotection under the action of HCl should return the desired amino alcohol **127** (or HCl salt).

A number of α-siloxy sulfinimines could be made by this route. Considering limitations in methods to effect dehydrative ring closure to forge bisoxazolines, a number of substituents were excluded from the library at what would ultimately become the 5-position of the oxazoline. These include *tert*-butyl, 4-methoxyphenyl and 4-CF_3-phenyl. Ultimately, a small subset of nucleophiles were evaluated. While yield was a concern, given that a late-stage, common intermediate was employed, diminished yields in the addition step would be acceptable;

however, excellent diastereoselectivity was required to avoid tedious chromatography. It should be noted that in the case of creating a library of bisoxazolines, the relative configuration is not necessarily critical as either an invertive or retentive dehydrative ring closure could be employed to provide the required final isomer.

Scheme 10. Synthetic approach to amino alcohols by 1,2-addition and late stage precursors.

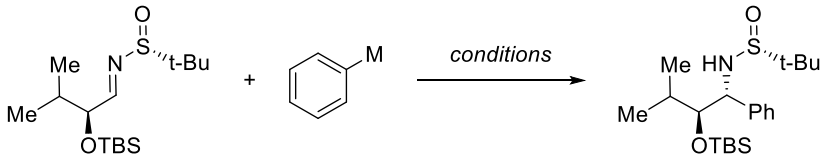


Initial optimization was inspired by the work from Ellman wherein α-siloxy (*R*)-sulfinimine **125** was used as a model system. When employing commercial phenylmagnesium bromide and non-coordinating CH_2Cl_2 as solvent, no conversion was seen at -40 °C (Table 6). Increasing the temperature resulted in 25% conversion to the desired product however in 88:12 d.r. Further increasing the temperature to 0 °C resulted in full consumption of the starting material but provided the product in an unacceptably low d.r. of 57:43. Changing the solvent to toluene provided satisfactory conversion at cryogenic temperatures, however the d.r. remained a problem. Gratifyingly this result confirmed a significant dependence of yield, conversion and diasteroselectivity on solvent. Changing to tetrahydrofuran, a polar coordinating solvent, also provided the desired product. Surveying temperatures it was found that at cryogenic temperatures, phenylmagnesium bromide provided 71% conversion with an increase in

diastereoselctivity from those observed in toluene, but this required extended reaction time that was unacceptable. Addition of TMEDA, which had previously been shown to increase the diastereoselectivity of the 1,2 addition of methylmagnesium bromide, had no effect on diastereoselctivity in this case. Changing the absolute configuration of the sulfonimine provided the corresponding product in a 77:33 d.r.

At this point it was clear that to obtain full conversion to the desired product while maintaining excellent diastereoselectivity, the conditions needed to be changed. Taking inspiration from Barrow, who demonstrated that alkyllithium reagents are competent nucleophiles to forge β-amino alcohols by 1,2-additon, phenyllithium was employed in this transformation. Gratifyingly, this change resulted in complete consumption of the starting material and provided the corresponding 1,2-addtion product in a 91:9 d.r. Furthermore, this transformation was complete in 24 h and could be run at -78 °C. The exact origin of this rate enhancement is however ambiguous. One possibility is the increased nucleophilicity of the aryllithium reagent compared to that of the analogous Grignard reagent. Alternatively, by changing the identity of the alkylmetal, the nature of the transition state might have changed. The consequence of this could be a lower activation energy and, as a result, a faster rate at lower temperatures. Finally, adding TMEDA did not change the resulting conversions or diasteroselectivities. The robustness of this transformation was verified on a 1.0 mmol scale. Phenyllithium (generated *in situ* from bromobenzene) was cleanly incorporated into the α-siloxy sulfinimine **125** derived from L-valine to afford **126** in 80% yield and 91:9 d.r. Global deprotection under the action of HCl in dioxane/methanol provided the β-amino alcohol **127** after basic workup in 81% yield.

Table 6. Optimization of diastereoselective 1,2-conjugate addition.



125 **126**

entry	M	solvent	temp, °C	conversion, %	d.r.
1	MgBr	CH_2Cl_2	-40	0	--
2	MgBr	CH_2Cl_2	-20	25	88:12
3	MgBr	CH_2Cl_2	0	100	57:43
4	MgBr	toluene	-60	80	82:18
5	MgBr	THF	-70	71	88:12
6	MgBr/TMEDA	THF	-70	68	87:13
7	MgBr	THF	-70	73	77:33**
8	Li	THF	-78	> 99	91:9
9	Li/TMEDA	THF	-78	> 99	91:9

**(*Ss, 2S*)-starting material

With this critical result in hand, a small selection of nucleophiles was examined to evaluate the efficacy of this transformation with a number of electronically and sterically diverse aryllithium species. Both 4-methoxyphenyllithium and 4-CF_3-phenyllithium were cleanly incorporated to afford the corresponding products **134** and **135** with a d.r. of 96:4 for both. Additionally, the aryl lithium derived from 2-methylbromobenzene via lithium-halogen exchange provided the corresponding product **133** in full conversion and 97:3 d.r. Employing the sulfonimine derived from ethyl lactate provided products **136 - 138** in full conversion and as a single diastereomer! At the time of writing, others have continued to expand the scope of this method to include benzyl nucleophiles, polyaromatics and alkyllithiums to evaluate the utility of this method to access large libraries of 1,2-amino alcohols for a training set, though these results are currently unpublished.

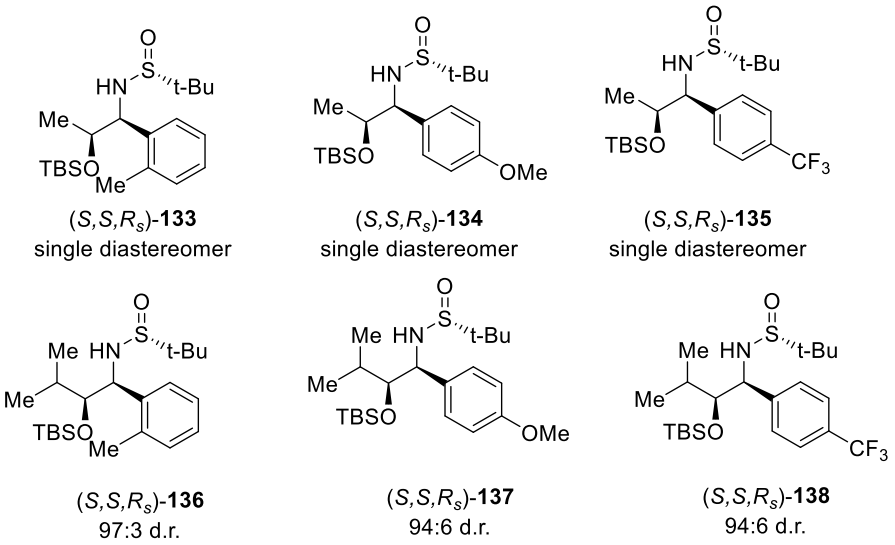


Figure 34. Initial survey of diastereoselective additions.

3.4.3. Stereochemical Models[76]

As previously mentioned, the effect of the α-siloxy stereogenic center inverted the diastereoselectivity observed from sulfinyl imines which lack this motif. The presence of the α-stereocenter also requires the consideration of matched and mismatched cases, which were shown to have a small but not insignificant effect on diastereoselectivity. Additionally, solvent was shown to have a drastic effect on the diastereoselectivity of the resulting products. Three stereochemical models have been proposed to explain the corresponding stereochemical outcome (Figure 35). The original Ellman proposal posits a chair-like transition state structure with an uncoordinated pendant siloxy group. The identity of the transition state becomes more ambiguous when the observed stereochemical outcome of the nucleophilic addition is opposite of that observed by Ellman. This change is stereochemical outcome is generally observed when a non-coordinating solvent is employed in the reaction (e.g. toluene, CH_2Cl_2). Furthermore, this change in stereochemical outcome was observed when phenyllithium was used as a nucleophile. Both transition states afford the same product.[74] The Davis transition state is postulated to provide the observed outcome through chelation of the oxygen by a Lewis acid (e.g. the Grignard reagent) which, in turn, blocks the *Si* face of the imine to give the observed selectivity. Alternatively, this same selectivity can be obtained through the 'Anti-Ellman' transition state. This relies on a pre-coordination of the pendant siloxy substituent to the organometallic nucleophile to create a bicyclic-chelated transition state. While this seems plausible, on closer

examination in order for this putative transition state to be operative an isomerization of the imine to the *Z*-configuration is required.

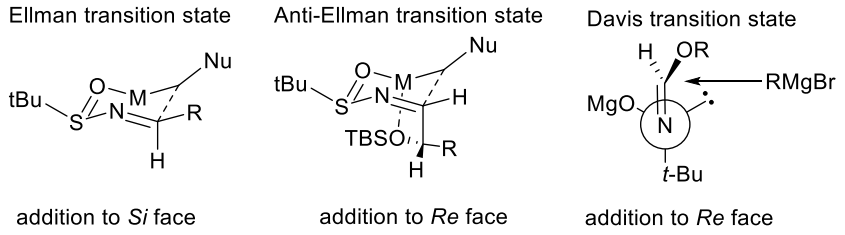


Figure 35. Transition state models for diastereoselctive 1,2-conjugate addition to sulfonimines.

This behavior has been established previously by Ellman during the course of investigating the 1,2-addition of aryl- and alkyllithium reagents to *N*-*tert*-butanesulfinyl imines in the presence of trimethylaluminum. During the course of the investigation, it was found that the ratio of the diastereoselectivities of the products exceeded the initial *E:Z* ratio of the starting imine. It was initially thought that pre-coordination to trimethylaluminum would alter the *E*:Z ratio to reflect that observed in the final product, however, subsequent NMR investigations found that there was no change in ratio from the parent imine.[77] Ultimately it was concluded that the selectivity is under Curtin-Hammett control. The ability of sulfinimines to undergo *in situ* isomerization was later studied computationally. It was found that the N-inversion barrier to isomerization was 18.7 kcal/mol, which compares well with experimentally validated results.[78] These smaller barriers of inversion for sulfinimines compared to simple imines are partially the result of ground state destabilization owing to steric repulsions between the sulfinyl group and the substituent that is *cis.*

3.4.4. Discussion and Outlook

This chapter describes a concerted and collaborative effort to identify a method to access large libraries of β-amino alcohols as precursors to numerous ligand classes including bisoxazolines. Initial approaches, while seemingly robust, encountered numerous problems including partial racemization of intermediates, lengthy synthetic sequences, and unknown relative and absolute sterochemistry. These challenges resulted in a herculean synthetic effort to access 40 bisoxazolines of which only 28 were ultimately made. During this time it was realized that not only was the approach to accessing amino alcohols inefficient but the computational

methods to select requisite bisoxazolines was fundamentally flawed and, as such, both components of the program required a new approach.

Numerous synthetic methods were evaluated to access diverse libraries and ultimately the 1,2-addition of aryl lithiums was identified as a viable approach to access the requisite libraries of amino alcohols. With that said, there were concessions that needed to be made. Namely, certain functional groups are not tolerated under the reaction conditions (e.g. –nitro, 1,2-dihalogented arenes) which is an inherent limitation in this approach. As a result, the *in silico* library has had to accommodate these limitations. As improvements to the scope of this transformation are found, corresponding computational methods to expand the *in silico* library should be developed without having to resynthesize a training set.

Additionally, while access to large libraries of amino alcohols is available, methods to access the corresponding bisoxazolines are still lacking. Indeed, early synthetic methods to affect both invertive and retentive closures of bis-β-amido alcohols to furnish the corresponding bisoxazolines were another major hurdle. Each putative ligand required optimization, especially those containing bulky substituents at what would ultimately become the 5-position. Identification of a mild, ubiquitous synthetic method to effect ring closure is a challenge that still needs to be overcome. With respect to accessing the requisite β-amino alcohols, there are still gaps in the optimization that have not been explored which could provide superior yields and selectivity. Specifically, an extensive solvent screen has never been performed employing aryl lithium nucleophiles. Given the obvious dependence of selectivity on solvent this should be examined. Additionally, it was assumed that the siloxy protecting group is necessary, however, no experiments have been conducted to examine the effect of first deprotonating the free alcohol followed by nucleophilic addition of the corresponding aryllithium. Not only could this provide increased (or inverted) diastereoselctivity, this approach would remove synthetic steps to access the requisite hydroxy sulfinyl aldimine. Lastly, the stoichiometry of sulfinimine and nucleophile has never been systematically examined. This, along with other general optimization, should be performed as the aryl/alkyl halide precursors can often be synthetically challenging to access.

In short, while a significantly improved approach to accessing large libraries of β-amino alcohols has been identified from existing literature, there is still much work to do. Most importantly, given the obvious synthetic overhead to accessing a library of bisoxazolines,

identifying a robust method to assess computational methods *prior* a large synthetic undertaking is paramount. While there are many methods to access β-amino alcohols, it is clear that methods to access large libraries on a synthetically useful scale are not as common. Through these efforts, access these libraries was identified and the scope of this method expanded; however, additional improvement and optimization are still required.

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Appendix A. Lewis Base-Catalyzed, Epoxide-Opening Cascade Reactions

A.1. Introduction and Rationale

> "… and all the water was changed into blood. The fish in the Nile died, and the river smelled so bad that the Egyptians could not drink its water. Blood was everywhere in Egypt. … And all the Egyptians dug along the Nile to get drinking water, because they could not drink the water of the river."
>
> Exodus 7:20-24 (NIV)

In 1981, a new class of natural products was isolated from the "red tide" dinoflagellate *Ptychodiscus brevis*. [79] Responsible for the toxic blooms that have resulted in mass die-offs of marine wildlife, these dinoflagellates produce the highly toxic natural product brevetoxin B (**139**). It is believed that the Bible contains the earliest written account of a red tide event as the first of ten plagues to afflict ancient Egypt.[80] In modern times, brevetoxin B is the causative agent of neurotoxic shell fish poisoning for those who are unlucky enough to consume contaminated shell fish.[81]

In the intervening years since the disclosure of the structure of brevetoxin B, significant effort has been made to further understand this class of natural products.[82] These studies continued effort toward isolating and characterizing related analogs, extraordinary multi-step synthesis, exploring the biosynthesis and biological function as well as development of synthetic methods to efficiently access the core of repeating THP rings. These efforts, which have arguably pushed the field of chemistry forward, have tested the boundaries of not only synthetic methodology and total synthesis but analytical methods as well. Indeed, the analogs that have been structurally characterized are nothing short of amazing in their complexity intertwined with their "exquisite and fascinating regularity".[80]

Congeners of brevetoxin B include some of the largest, and most complex natural products discovered to date. Maitotoxin **140**, which contains 32 ether rings, 22 methyl groups and 28 hydroxyl groups is the largest, non-polymeric, natural product discovered to date. The structure was ultimately solved through extensive NMR studies, partial chemical synthesis and chemical degradation although there has been some dispute if this structure is indeed correct.[83–85] Nevertheless, the unprecedented size, complexity and potent biological activity of this natural product has garnered much attention. Numerous other ladder polyethers of the same class have been characterized. Each member contains a conserved pattern of fused five to nine-membered

cyclic fused cyclic ethers bearing a *trans-syn-trans* stereochemical arrangement around the ring which continues throughout the entire core of the structure (Figure 36). Although members share a conserved pattern, their biological functions can be varied. Notable members of this class of natural products include brevetoxin A **141**, ciguatoxin 3C **142** and gambierol **143**, all of which have been used as probes of protein structure and function and are extremely toxic.[86] Although other members, including gymnocin-A **144**, have demonstrated anti-cancer activity.[87] Finally, and perhaps most interestingly, brevenal **145** has been shown protect fish from the toxic effects of brevetoxins.[88] Brevenal and the synthetic analog β-naphthoyl-brevetoxin-3 also inhibit bronchoconstriction and prevent a decrease in tracheal mucus velocity which could have applications treating mucociliary dysfunction commonly found in patients with cystic fibrosis.[89] Although the exact mechanism of action for any of the ladder polyethers has not been described definitively, it is known that brevetoxins target voltage-sensitive ion channels which results in the observed neurotoxicity. Other members of this family are presumed to act on different ion channels, this has not yet been proven conclusively.

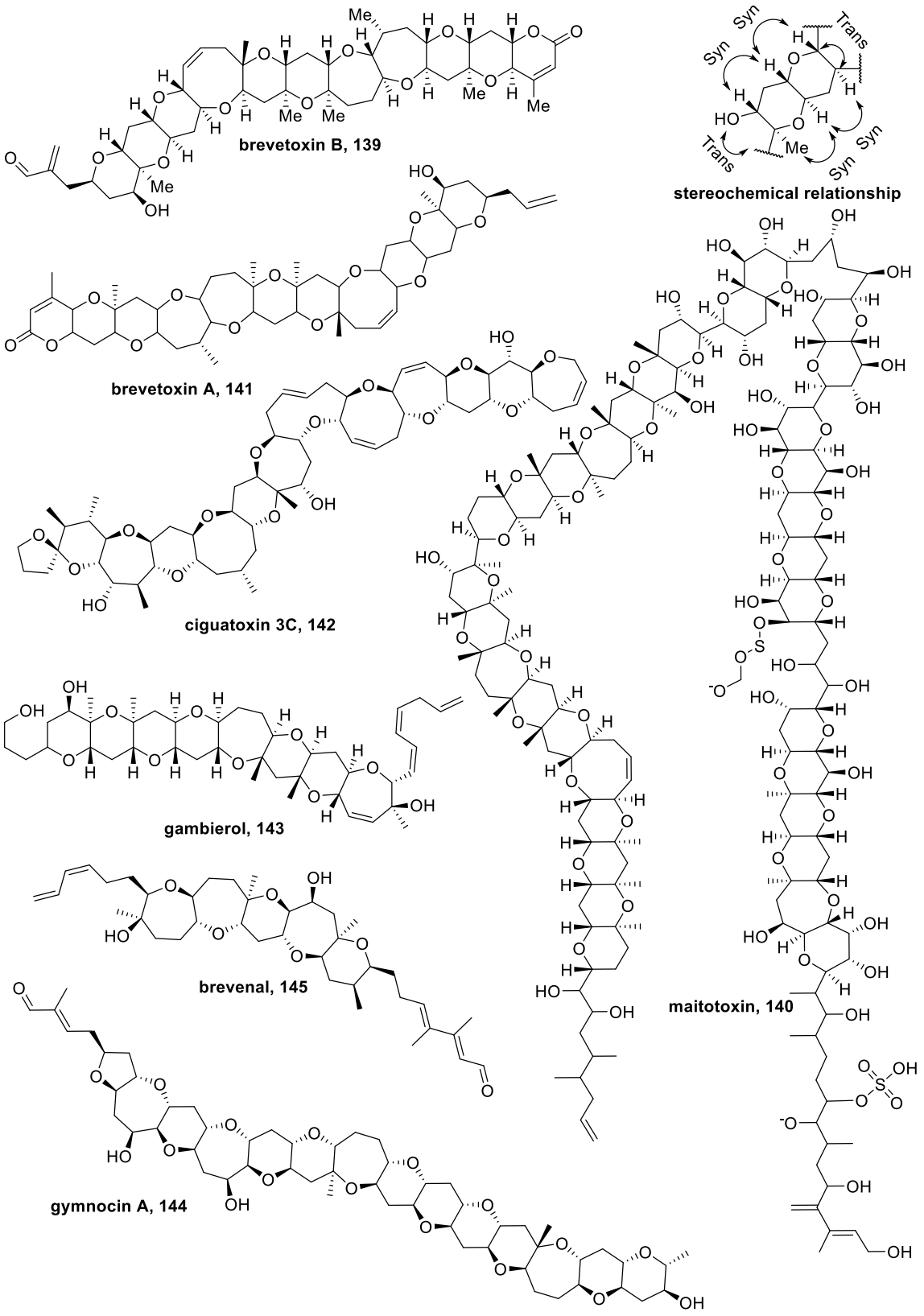


Figure 36. Select structures of ladder polyethers and their sterochemical arrangement.

The extreme potency and complexity of the ladder polyether class of natural products has naturally led to questions about their biosynthetic origin.[90] In 1983, Cane, Celmer and Westley proposed a biosynthesis for monensin derived from a single cascade reaction; specifically, an epoxide-opening cascade which provides the fused ring system.[91] This model was later the inspiration for the biosynthetic proposal applied to brevetoxin B, proposed independently by Shimizu and Nakanishi depicted in Figure 37. [92,93] It is likely that these polyepoxide substrates arise through a mixed polyketide/terpenoid biosynthetic pathway. Ultimately, through a cascade of nucleophilic expoxide ring openings, the C-C-O pattern of connectivity and the *trans-syn-trans* ring junction geometry is established.[92] A retrobiosynthetic analysis conducted by Spencer and coworkers found that, assuming the polyepoxide precursors are involved in the biosynthesis, all of the epoxides must be stereochemically identical (Figure 37). That is to say, all of the epoxides in the system need to be either (*R*,*R*) or *(S*,*S*), trans epoxides.[85] This insight suggests that a single, ubiquitious monooxygenase may be involved for the biosynthesis of these natural products. Although this hypothesis is attractive in its elegance and feasibility, it should be noted that to form the contiguous tetrahydropyran (THP) system the epoxides must cyclize in a *disfavored* 6-endo fashion. Certain classes of ionophores undergo a 5-exo ring opening to provide a series of linked tetrahydrofurans but, to date, no hypothesis that provides a satisfactory explanation for the observed ring opening sequence has been put forth.

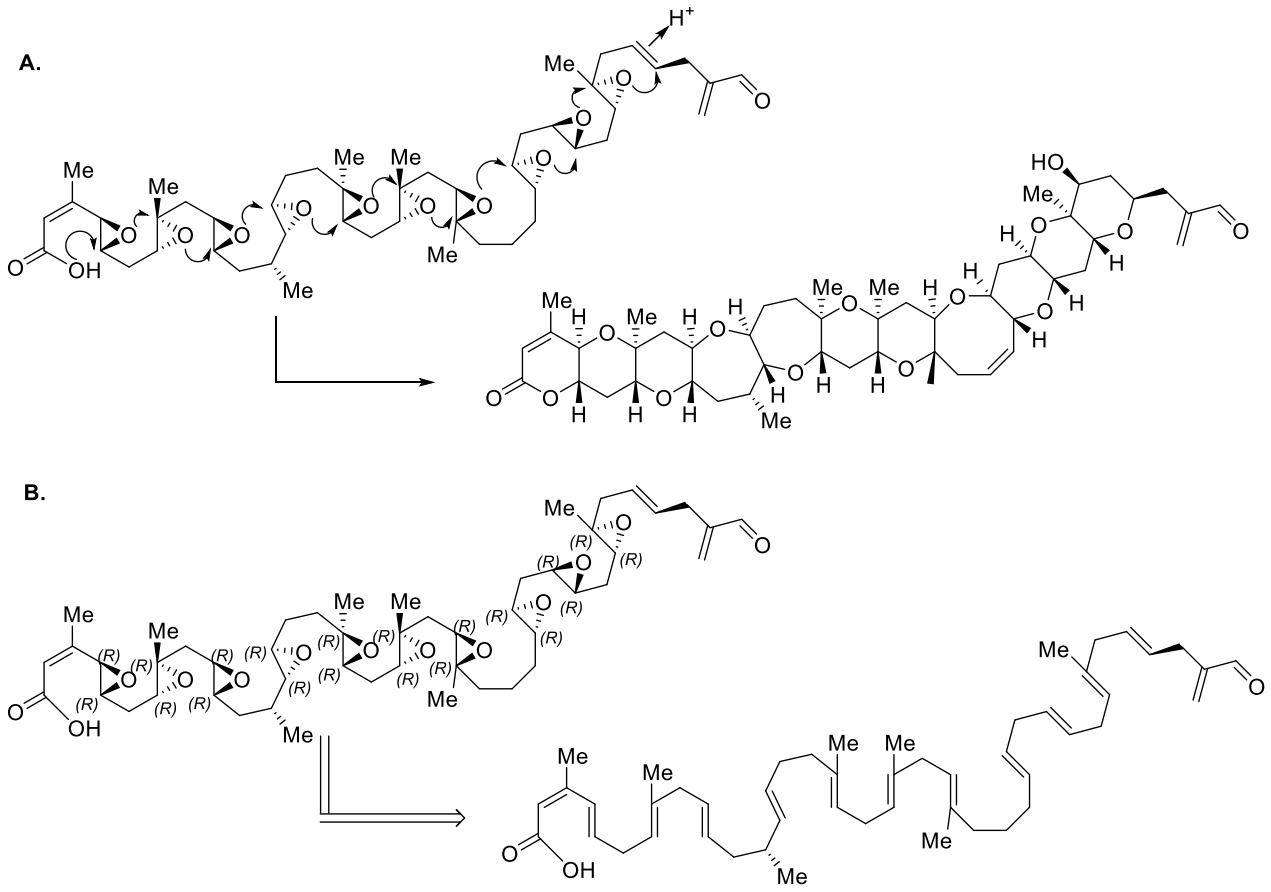
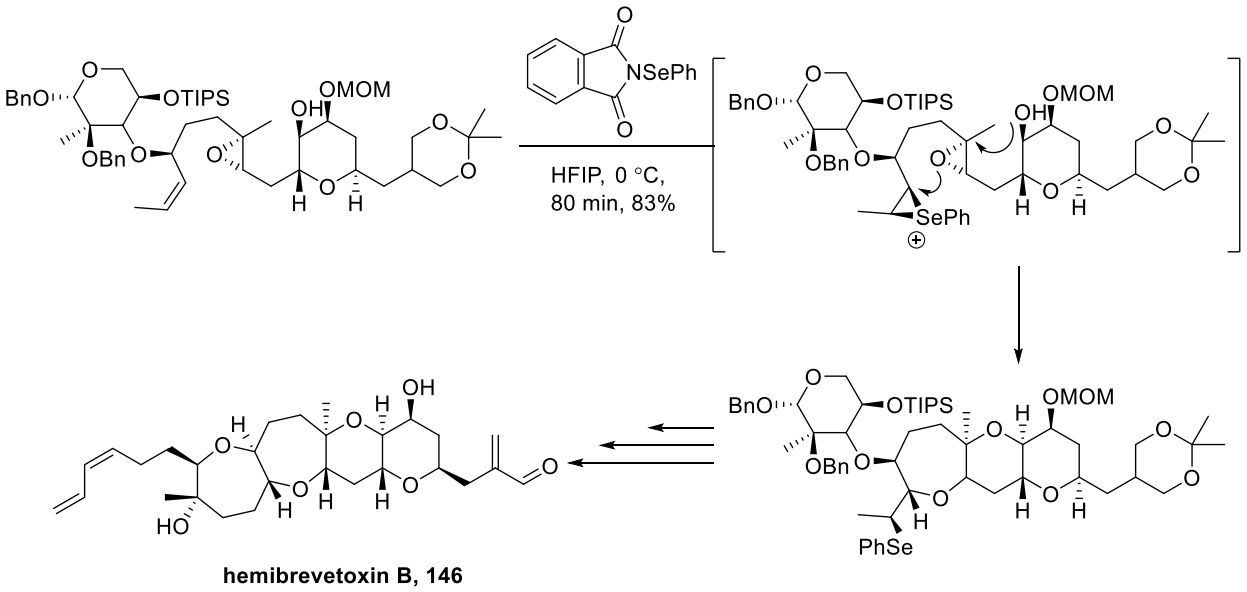


Figure 37. (A) Biosynthetic proposal by Shimizu and Nakanishi (B) Retrobiosynthetic analysis by Spencer.

Even prior to the proposed biosynthesis, synthetic chemists had already started working on synthetic efforts. Given that K.C. Nicolaou described brevetoxin B as "love at first sight" it is no surprise that by the summer of 1982 he had secured funding from the National Institutes of Health for a total synthesis.[80] Twelve years later, on October 20th 1994, the total synthesis of brevetoxin B was completed (Nicolaou was informed by fax as he was away from the lab!).[94–96] The synthesis was completed in a remarkable 123 steps with an average yield per step of 91%. Since then, a number of synthetic efforts have bene undertaken to access brevetoxin B and other members of the ladder polyether class. In 2004, Nakata and coworkers again completed the synthesis of brevetoxin B, this time in an efficient 90 steps and overall yield of 0.14%.[97] Other syntheses include brevetoxin A, gambierol, gymnocin-A and gymnocin B.[98–102] Of particular interest is Holton's total synthesis of hemibrevetoxin B **146** in which employs seleniranium ion

formation to initiate a directed cascade to forge two ether rings in a single operation as a single diastereomer (Scheme 11).[103]

Scheme 11. Holton's synthesis of hemibrevetoxin B employing a selenaranium ion initiated cascade.



As interest in the biological activity and total synthesis of these molecules has increased, so have efforts to develop efficient methods to more efficiently access the THP core.[104] Several methods focus on the development of epoxide cascade reactions to efficiently construct multiple ring structures in a single step.[105,106] As mentioned previously, the key challenge is overcoming the disfavored 6-endo ring formation. Numerous methods have been developed to favor the 6-endo S_N2 type attack and largely relying on directing groups. For example, Murai and workers reported the epoxide cascade described in Figure 38, entry 1.[107] The pendant methyl ether serves to coordinate the La^{3+} Lewis acid, acting as a directing group and disfavoring the spiro transition state observed in the 5-exo opening. McDonald and coworkers reported that installation of methyl groups was sufficient to favor the 6-endo ring closure by stabilizing positive charge at the site of attack (Figure 38, entry 2).[108] The inherent problem with these methods, and others, is that the directing group cannot be removed thereby limiting the utility of the method; however some methods have been developed with traceless directing groups. [109,110]

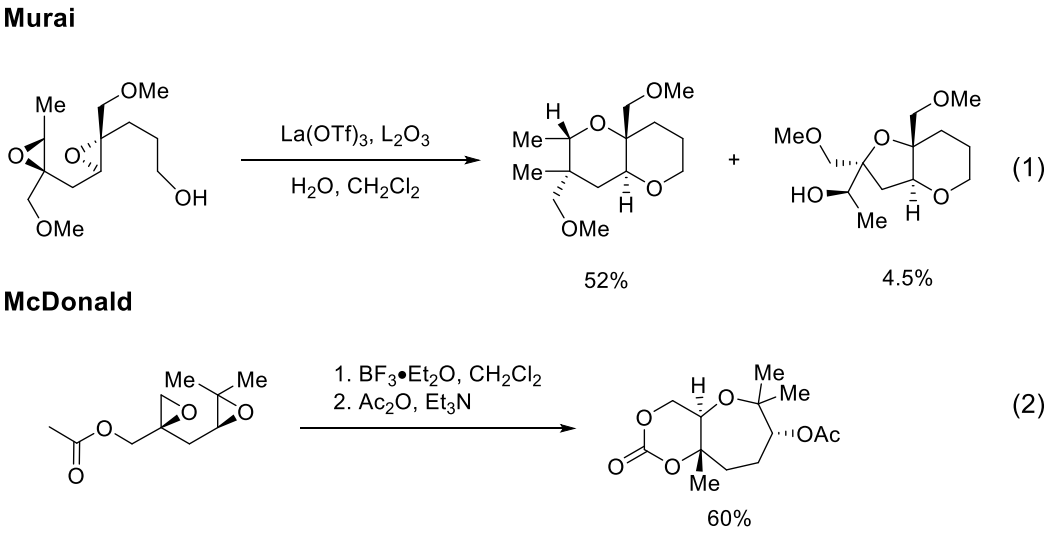


Figure 38. Select methods to favor endo-opening of epoxides.

More recently, Jamison and coworkers disclosed a remarkable finding that by preforming the first THP, and conducting the cascade reaction in neutral water, the 6-endo ring opening is favored without the directing group present.[86,111] It was reasoned that by prepositioning the first THP, the entropic factors that normally favor the sprio transition state would be minimized (Figure 36). Instead, enthalpic contributions would play a larger role thereby favoring the fused transition state. By templating the first THP ring, cascades of both two and three epoxides (resulting in three and four fused ring systems, respectively) are efficiently accessed in good yields (Figure 39). An in depth kinetic investigation found that the epoxide opening cascade occurs by a stepwise mechanism rather than through a concerted cascade.[112] Surprisingly, the first ring formation occurrs slowly and with only a 2:1 endo:exo selectivity. However, it was found that the second and final ring closure is significantly faster and proceeds with a surprising 15:1 *endo*:*exo* selectivity. Importantly, no evidence to support a concerted pathway is favored. These stunning results are attributed to both the templating of the first THP and the effect of neutral water. Rather than acting as a simple Brønsted acid, water is serving as a bifunctional promoter to activate both the hydroxyl and epoxide through a hydrogen bonding network.

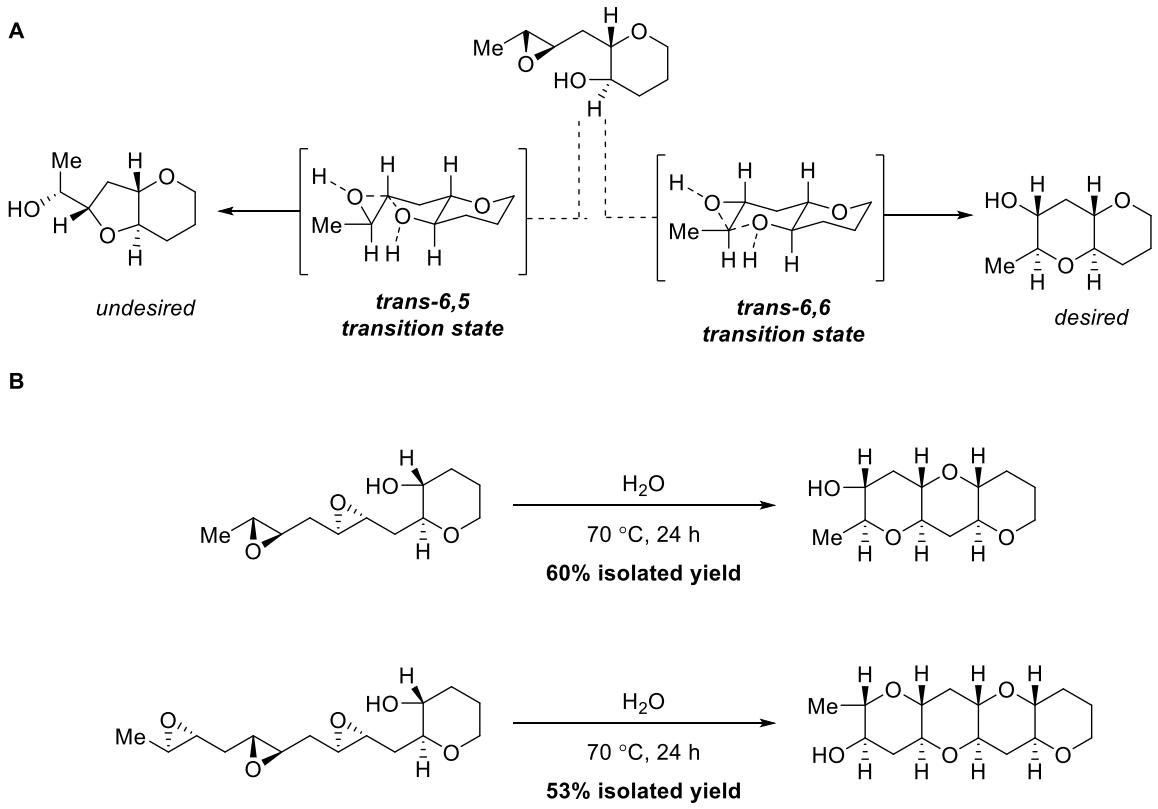


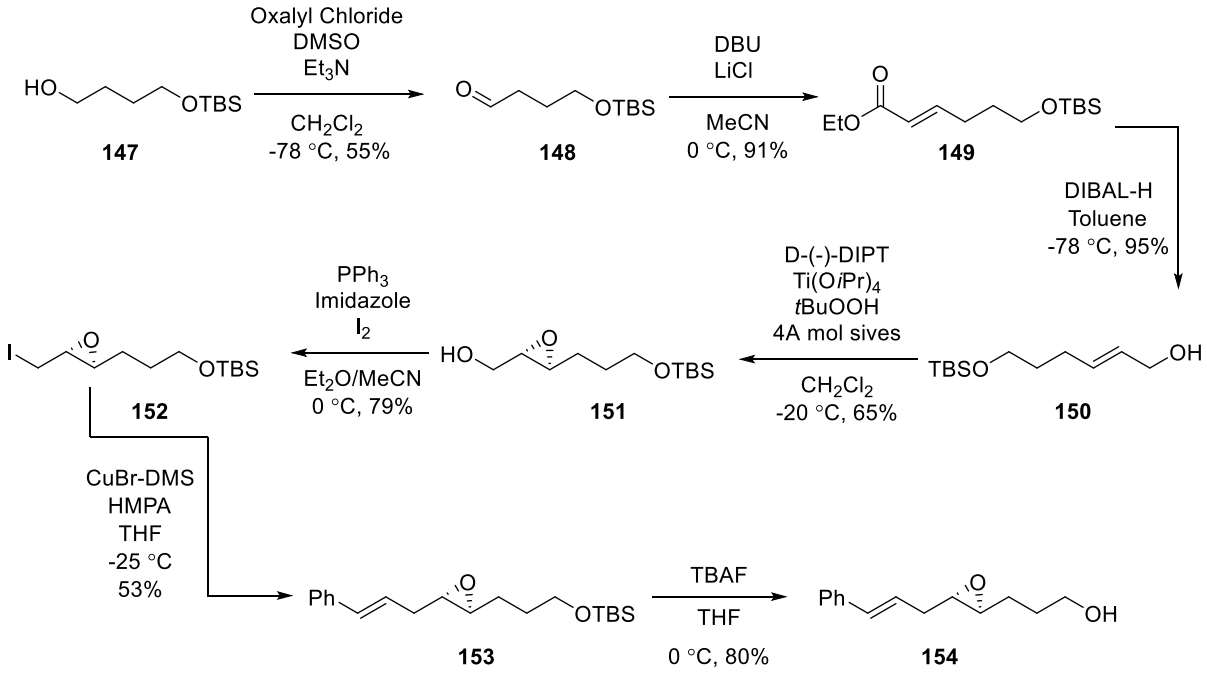
Figure 39. (A) Favored and disfavored transition states in the templated epoxide opening. (B) Products of the templated epoxide opening.

Inspired by these exciting results, it was envisioned that a thiiranium ion accessed by Lewis base activation of Lewis acids, would serve to initiate this cascade reaction. A number of advantages were envisioned by employing this strategy. First, a thiiranium ion would likely direct the order of ring closure. Failure to do this was problematic in previous investigations as incomplete and undesired cyclization products as well as ring opened products were often found. By initiating the cascade with a highly reactive thiiranium ion, this problem would be avoided. Additionally, the resulting thioether would serve as a convenient functional handle to combine fragments in a total synthesis or drug discovery campaign. Lastly, because the stereochemistry of the thiiranium ion would have to match that of the epoxides present, this would be trivial given the excellent selectivity of the Lewis base catalysts developed in the Denmark Laboratories.

A.2. Substrate Synthesis and Performance

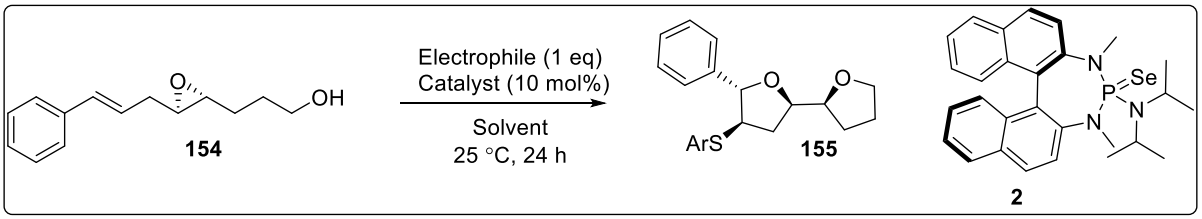
Synthesis of the required test substrate began with Swern oxidation of known alcohol **147** providing the corresponding aldehyde **148**. Elaboration under Horner-Wadsworth-Emmons conditions provided the unsaturated ester **149**. Reduction and subsequent oxidation employing Sharpless' conditions provided epoxy alcohol **151** in good yield and enantioselectivity. Conversion of **151** to the corresponding iodide **152** provided the requisite precursor for a copper-mediated displacement. Treatment of **152** with phenylmagnesium bromide and CuBr-DMS in HMPA/THF mixture afforded **153** in modest yield. Finally, deprotection under the action of TBAF returned the desired substrate **154** to begin preliminary investigations.

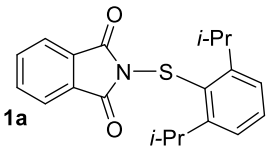
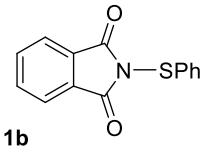
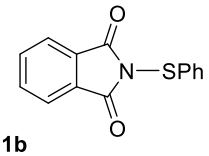
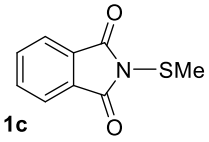
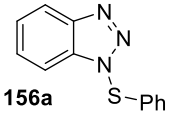
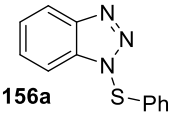
Scheme 12. Synthetic route to access substrate **154**.



Initial optimization began by employing sulfenylating agent **1a** in HFIP with catalyst **2**. Although the desired reaction to access **155** was observed, conversion was slow. Additionally, the d.r. of **155** was disappointingly low. Attempting to increase the rate of the reaction, sulfenulating agent **1b** bearing a simple phenyl group was used. Although the conversion did in fact increase to 75% in 24 h, the d.r. of **155** was lower. The enantiomer of catalyst **2** was used to examine the effects of a matched/mismatched case, however there was little effect. This same degradation in d.r. was observed using sulfenylating agent **1c** bearing a methyl group.

Table 7. Optimization of the Lewis base mediated epoxide cascade reaction.



entry	sulfenylating agent	solvent	conversion (%)	time (h)	d.r. [1]
1	 **1a**	HFIP	45	24	85:15
2	 **1b**	HFIP	75	24	80:20
3	 **1b** (R-catalyst)	HFIP	75	24	77:23
4	 **1c**	HFIP	93	24	75:15
5	 **156a**	HFIP	quant.	5	50:50
6	 **156a**	TFE	85%	24	80:20

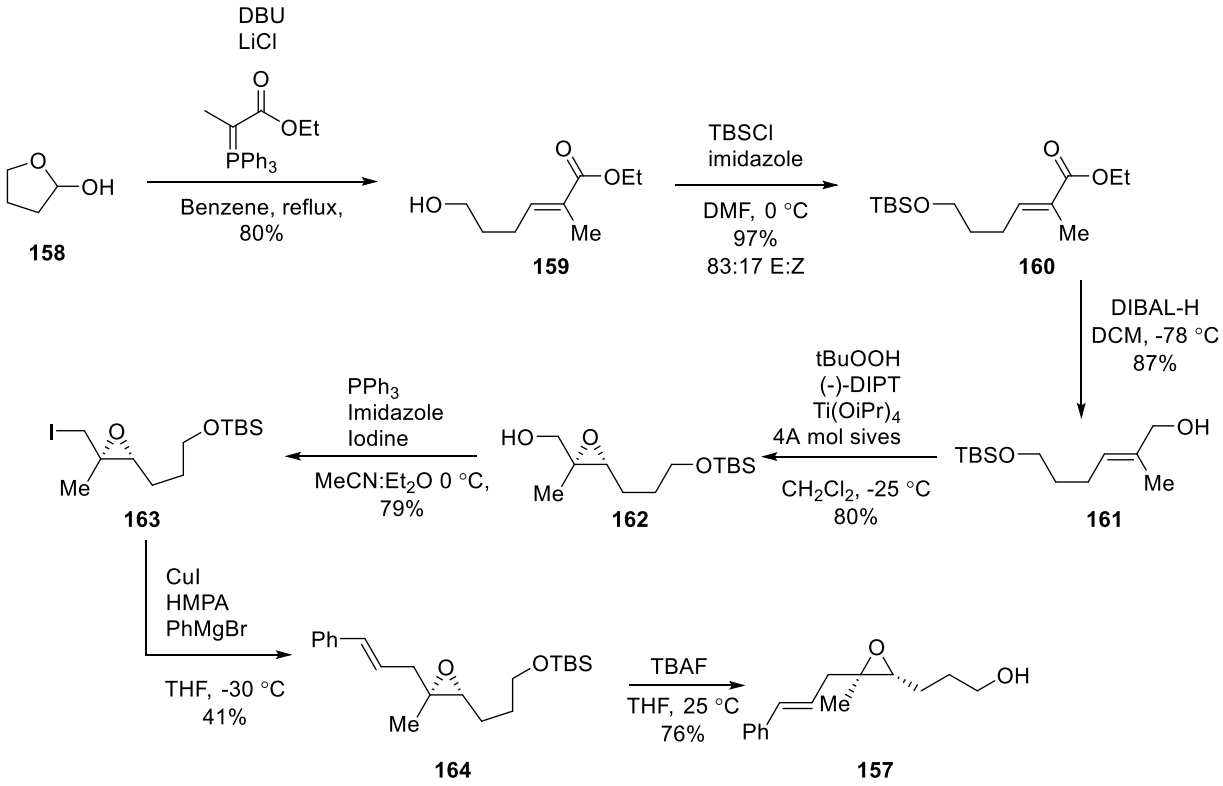
1. Determined by ^{1}H NMR analysis.

In an effort to increase the rate of the reaction, more active sulfenylating agent **156a** was chosen. Although this did provide full conversion to the desired product, a d.r. of 1:1 was observed indicating only background reaction in HFIP. In an attempt to suppress the background reaction 2,2,2,-trifluoroethanol was used. This solvent did suppress the background reaction and

a d.r. of 80:20 was observed with full conversion. It was anticipated that a version of this sulfenylating agent bearing substituents on the arene would increase the d.r. but it was unclear how this would affect the rate. However, it was still unclear the effects adding a methyl group would have on favoring the formation of the fused THP system.

To identify the effects of adding a methyl group, substrate **157** was designed and accessed via the route in Scheme 13. Compound **158** was directly converted to ethyl ester **159** in one step. Alternative methods were explored to avoid the tedious chromatography associated with separating olefin isomers; however, this route was sufficient to generate enough material to assess the directing ability of an additional methyl group. Protection and subsequent reduction to alcohol **161** followed by asymmetric epoxidation furnished epoxide **162**. Repeating the same sequence, Appel conditions gave the requisite iodide **163** for copper-mediated displacement to provide **164** which, after TBAF-mediated deprotection, afforded the targeted substrate **157**.

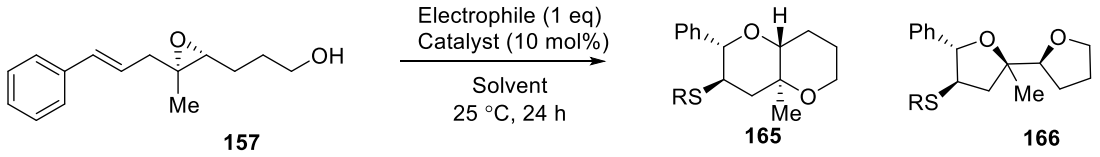
Scheme 13. Synthetic route to access substrate **157**.

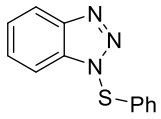


Upon subjecting **157** to the reaction conditions, the desired directing effect from the methyl group was observed resulting in a 65:35 product ratio of **165** and **166**. Although this

proof of concept was interesting, given the lengthy synthetic sequences to access starting materials and the exceptionally difficult chromatography to separate **165** and **166** in the reaction mixture, it was decided that this project should be abandoned.

Table 8. Thiiranium initatied cascade reaction with directing methyl group.



entry	sulfenylating agent	Solvent	Conversion (%)	time (h)	product ratio (**165**:**166**)
1		TFE	45	24	65:35

Though the results for the desired transformation were disappointing, this class of transformations still holds promise. Initiation by thiiranium ion formation to form a series of tetrahydrofurans could easily be applied to a number of ionophore natural products which have been evaluated as potent antibiotics. More broadly, this study demonstrates that the HFIP system is mild enough to be extended beyond simple olefins or polyenes. Additionally, alternative transformations could be envisioned wherein an epoxide first opens the thiiranium ion and a subsequent, intermolecular nucleophile intercepts the resultant oxonium ion.

Appendix B. Lewis Base-Catalyzed Functionalization of Allenes

B.1. Introduction and Rationale

In an effort to extend the scope of the Lewis base activation of Lewis acids past electron rich and neutral alkenes, an investigation into the competency of simple allenes was undertaken. The reactivity of allenes is distinct from those of alkenes and silylenolethers given the two cumulated carbon-carbon double bonds. Numerous novel reactions have been developed to functionalize allenes including transition metal mediated, electrophilic cyclization reactions. These methods have enabled allenes to serve as precursors for various heterocyles, three carbon units in cycloaddtions, and natural product total synthesis. [113–115]

Various electrophilic transformations involving the formation of haloranium, selenaranium and thiiranium ions have been reported. 1,2-allenyl sulfoxides have been demonstrated to undergo electrophilic addition with I_2 in acetic acid (Figure 40). The corresponding vinyl iodide was generated in low yield but with excellent regio- and stereoselectivity.[116]

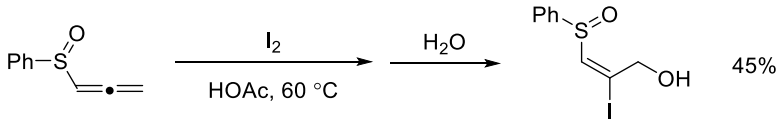


Figure 40. Formation of viyl iodides from Allenes.

An analogous transformation was described employing highly electrophilic phenylselenyl chloride to access the corresponding 1,2-allenic sulfoxides in moderate to excellent yield (Figure 41).[117]

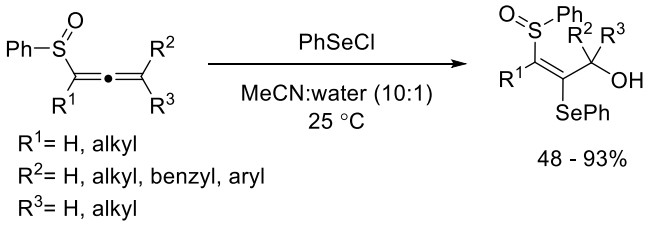


Figure 41. Electrophilic selenylation of allenes.

Of particular interest is the ability of vinyl sulfides (or the corresponding sulfones) to engage in transition metal mediated cross coupling reactions. Although employing vinyl sulfides in cross coupling methods remains challenging, particularly in comparison to vinyl halides, a number of methods have been developed to utilize these motifs. These include the nickel-mediated Kumada cross coupling described by Takei and coworkers (Figure 42, entry 1).[118] Other examples include the cross coupling of the corresponding vinyl sulfones has been described by Julia (Figure 42, entry 2) and the coupling of α-keto sulfones, potentially proceeding through a β-oxido vinyl sulfone (Figure 42, entry 3).[119–121] Given the excellent precedent of irranium ion formation with allenes, as well as the potential synthetic utility of the products, it was prudent to evaluate these carbon-based nucleophiles.

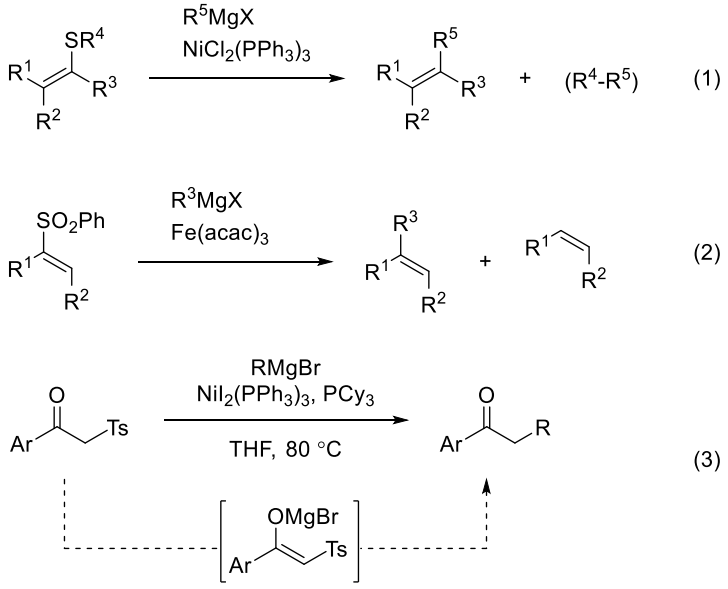


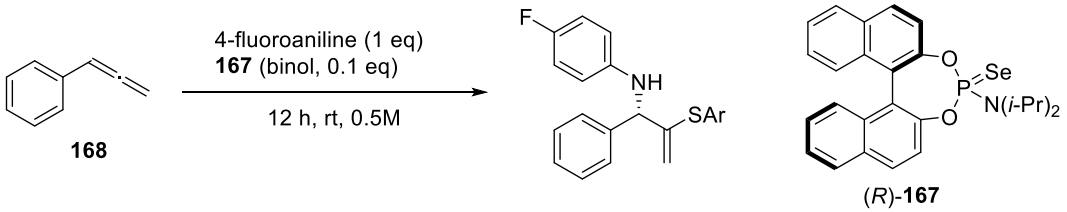
Figure 42. (1) Ni-mediated cross coupling of vinyl sulfides. (2) Fe-mediated cross coupling of vinyl sulfones (3) Ni-mediated cross coupling of α-keto sulfones.

B.2. Evaluation of Conditions

It was anticipated that the more electrophilic Lewis Acid-Lewis base complex generated by employing the BINOL-derived Lewis Base catalyst **167** would be required to successfully form the requisite thiiranium ion from the comparatively less nuclophilic allenes. Starting with allene **168** and subjecting to optimized conditions from the intermolecular functionalization of alkenes resulted in full decomposition of the starting material however no desired product

formation was observed. Employing TFE also returned the same decomposition results. Surveying different sulfenylating agent and product solvent combinations continued to return non-specific decomposition of the allene starting material. Subjecting allene **168** to similar protic conditions again resulted non-specific decomposition, therefore it was concluded that aprotic solvents would be required to successfully functionalize allenes.

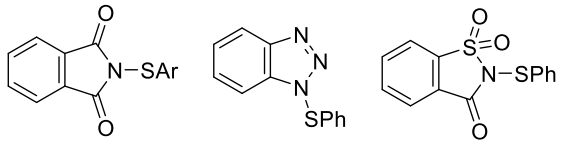
Table 9. Survey of reaction conditions to functionalize allene **168.**



168 (*R*)-**167**

entry	solvent	sulfenylating agent	yield (%)	remaining starting material (%)[a]
1	HFIP	1a	0	0
2	TFE	1a	0	0
3	EtOH	168	0	0
4	TFE	156	0	0
5	TFE	169	0	0

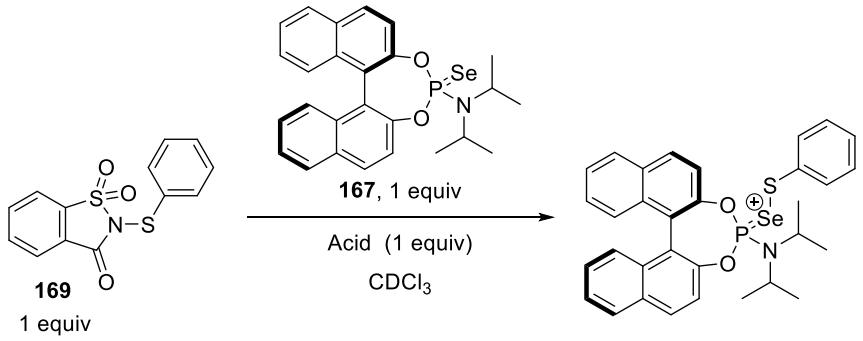
[a] determined by ^{1}H NMR analysis



1a **156** **169**

It was unknown the strength of acid required to activate any sulfenylating agent to form the Lewis acid-Lewis base cationic complex with **167**. Subjecting equimolar **167**, saccharin derived sulfenylating agent **169** and different acids, the formation of the acid-base complex was characterized by ^{31}P NMR. Sulfenylating agent **169** was chosen as it was likely that weaker acids would be required to form the Lewis acid-Lewis base complex thus enabling a broader scope of allenes in the future. Ultimately it was found that trichloroacetic acid was necessary to promote the formation of the Lewis acid-Lewis base complex (Table 10).

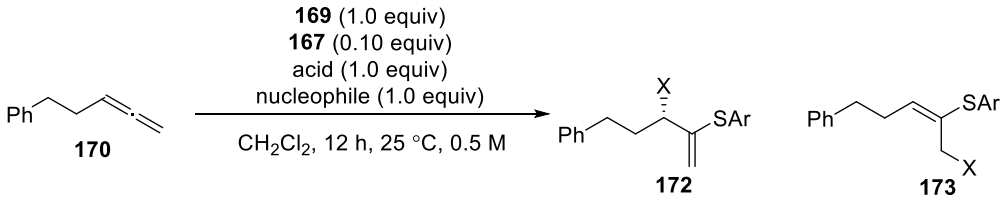
Table 10. Survey of acids to form the active, cationic complex with **167** and **169.**



entry	acid	pKa	result
1	-	-	no formation
2	acetic acid	4.76	no formation
3	chloroacetic acid	2.68	no formation
4	trichrloroacetic acid	0.65	complete formation
5	trifluoroacetic acid	-0.25	complete formation

Subjecting allene **170** to the conditions described in Table 11, entry 1 did not provide the desired amide **171** corresponding to acetamide capture but rather provided the corresponding oxyfunctioanalized allenes **172** and **173** in a 74:26 ratio as a result of ring opening from the carboxylate salt (Table 11). This result encouraged the survey of different nucleophiles to preferentially intercept the thiiranium ion intermediate. Unlike the intermolecular functionalization, the conjugate acids of the putative nucleophiles must be sufficiently acidic to not be protonated under reaction conditions.

Table 11. Attempts to functionalize allene **170**.



entry	nuclophile	desired product **171** (%, X = Nu)	**172:173** (yield, %) (X = acid)
1	acetamide	0	76:24 (36, 19 i.y.)
2	t-Bu-Carbamate	0	75:25
3	benzenesulfonamide	0	75:25
4	t-Bu-Carbamate	0	75:25
5	Phthalimide	0	75:25
6	benzamide	0	75:25

Unfortunately, no suitable nuclophiles were identified. *tert*-Bu-Carbamate, benzensulfonamide, phthalimide and benzamide did not successfully intercept the thiiranium ion. Rather, in all cases, the oxysulfenylation product was found. This is likely due to the fact that the conjugate base acts as the counter ion to the Lewis acid-Lewis base complex, and is inherently brought into proximity to the reactive thiirnaium ion enabling a faster rate of nucleophilic ring opening despite comparitivly lower nuclophilicity. In light of these results, and the poor regioselectivity observed in the oxysulfenylation side products, it was deemed that while there was some evidence of successful functionalization, the results did not warrant continuing to investigate this class of substrates.

Experimental

General Experimental

Reaction solvents tetrahydrofuran (Fisher, HPLC grade, BHT stabilized), diethyl ether (Fisher, ACS grade, BHT stabilized), and dichloromethane (Fisher, HPLC grade, not stabilized) were dried by percolation through two columns packed with neutral alumina under positive pressure of argon. *N*,*N*-dimethylformamide (Fisher, ACS grade) was dried by percolation though two columns packed with molecular sieves. Methanol and ethanol were distilled from magnesium turnings under a nitrogen atmosphere. Triethylamine was distilled from calcium hydride under a nitrogen atmosphere. Solvents for filtration, transfers, chromatography, and recrystallizations were purchased from commercial sources and used as received. "Brine" refers to a saturated solution of sodium chloride in distilled water. Column chromatography was performed using Merck grade 9385, 60 Å silica gel. Visualization was accomplished by UV light, potassium permanganate solution, ceric ammonium molybdate solution. Analytical TLC was performed on Merck silica gel plates with F_{254} indicator. Rf values reported were measured using a 10 x 2 cm plate.

^{1}H and ^{13}C NMR spectra were recorded on a Carver-Bruker 500 MHz (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometer. Spectra are reference to residual chloroform (δ = 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C), residual methanol (δ = 3.31 ppm, ^{1}H; 49.0 ppm, ^{13}C) or residual DMSO (δ = 2.50 ppm, ^{1}H; 39.52 ppm, ^{13}C). Chemical shifts are reported in parts per million. Assignments were obtained by reference to COSY, HMQC, HMBC, and NOESY correlations. Elemental analysis was performed by the University of Illinois Microanalysis Laboratory. Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI) spectra were performed at 70 eV using methane as the carrier gas on a Finnagin-MAT C5 spectrometer. Electrospray Ionization (ESI) spectra were performed on a Micromass Q-Tof Ultima spectrometer. Data are reported in the form of m/z (intensity relative to the base peak = 100). Infrared spectra (IR) were recorded neat on a Perkin-Elmer FT-IR system and peaks were reported in cm^{-1} with indicated relative intensities: s (strong, 0-33% T); m (medium, 34-66% T); w (weak, 67-100% T). Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus in sealed tubes and are not corrected.

Experimental for Chapter 2

The following commercial reagents were used as received: *n*-butyllithium (solution in hexanes), sodium borohydride, hexafluoroisopropanol, dimethyl sulfate, hexachloroethane, carbon dioxide (bone dry), lithium (granules), methyltriphenylphosphonium bromide, palladium on carbon (10%), 1-(4-aminophenyl)ethan-1-one **19a**, ethyl 4-aminobenzoate **18a**, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **20a**, pyridin-2-amine **21a**, phenylmethanamine **22a**, 2-tolylmethanamine **23a**, (4-(trifluoromethyl)phenyl)methanamine **25a**, 4-(aminomethyl)benzonitrile **26a**, furan-2-ylmethanamine **27a**, (*E*)-prop-1-en-1-ylbenzene **6**, styrene **29a**, *trans*-4-octene **37a,** (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene **33a**, and 3,5-dinitrobenzoyl chloride.

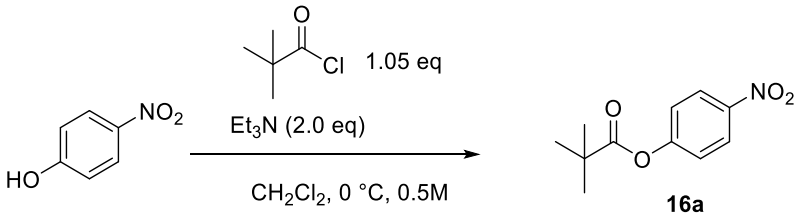
The following commercial reagents were purified prior to use: 4-Iodoaniline **11a** (recrystallized from boiling hexanes), 4-bromoaniline **12a** (sublimation), 4-fluoroaniline **13a** (vacuum distillation), 2-iodoaniline **14a** (recrystallized from boiling hexanes), 4-methoxyaniline **10a** (sublimation), 4-aminophenol **15a** (sublimation), (4-methoxyphenyl)methanamine **24a** (vacuum distillation), acetaldehyde (distillation), 2-chloro-1-methylpyridinium iodide (recrystallized from acetone).

Literature Preparations

The following compounds were prepared by literature methods and characterization matched the data previously reported: *tert*-butyl (4-aminophenyl)carbamate **17a**,[122] 1-fluoro-2-vinylbenzene **30a,**[123] 1-methyl-2-vinylbenzene **31a,**[123] (3-methylbut-1-en-1-yl)benzene **32b,**[124] 2-(prop-1-en-1-yl)naphthalene **34b,**[125] 3-(prop-1-en-1-yl)-1-tosyl-1*H*-indole **35b,**[126] 3-vinylthiophene **36a**[127] and Lithium 4,4′-Di-tert-butylbiphenylide (LiDBB),[128] 2-((2,6-diisopropylphenyl)thio)isoindoline-1,3-dione**,**[129] and (*S*)-**5**[129], Dichloro Bis(acetonitrile) Palladium.[130]

Preparation of Starting Materials

Preparation of 4-Nitrophenyl Pivalate (16a)



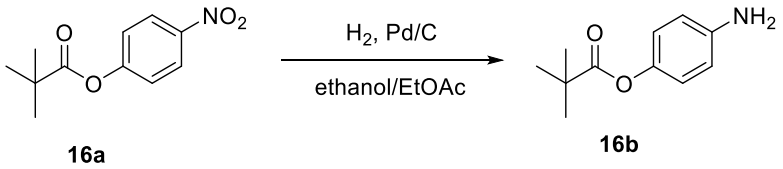
A flame-dried, 100-mL, round-bottomed flask fitted with a Teflon stir bar, internal digital thermometer and gas adapter fitted with rubber septum under an argon atmosphere was charged with 4-nitrophenol (1.40 g, 10.0 mmol) and CH_2Cl_2 (20 mL). Triethylamine (2.8 mL, 20 mmol, 2.0 equiv) was added in a single portion at 23 °C resulting in the formation of a bright yellow solution. The reaction was cooled to an internal temperature of 2 °C in an ice/water bath. Pivaloyl chloride (1.3 mL, 11 mmol, 1.05 equiv) was added dropwise via syringe. The reaction was maintained in the ice/water bath and monitored by TLC (hexanes/EtOAc, 9:1). After complete consumption of the starting material, water (15 mL) was added, and the reaction mixture decanted into a 125-mL separatory funnel. The flask was rinsed with CH_2Cl_2 (2 x 10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (20 mL), and were then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford 2.10 g (94%) of **16a** as a white solid that was sufficiently pure to carry onto the next step. The spectroscopic data for **16a** matched the literature values.[131]

Data for **16a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

8.34 – 8.22 (m, 1H), 7.32 – 7.23 (m, 1H), 1.40 (s, 9H).

Preparation of 4-Aminophenyl Pivalate (16b)



16a **16b**

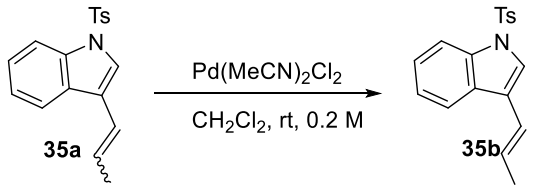
A 55-mL test tube (25 x 150 mm) with Teflon stir bar was charged with **16a** (2.10 g, 9.4 mmol), ethanol (5 mL) and EtOAc (10 mL). Palladium on carbon (10%, 51 mg, 0.48 mmol, 0.05 equiv) was added in a single portion to the reaction. The test tube was placed in a high pressure bomb (3 x 15 cm internal, rated for 400 psi) and sealed. The bomb was charged with hydrogen gas (250 psi) and slowly vented. This process was repeated three times. The bomb was then charged with hydrogen gas (250 psi), sealed, and placed on a magnetic stirrer. After 12 h the gas was slowly vented and the reaction mixture filtered over Celite, washed with EtOAc (2 x 20 mL), and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford **16b** as white solid. The product was purified by trituration as follows. The crude material was suspended in diethyl ether (20 mL) and sonicated at 23 °C and cooled to -20 °C for 30 min. Vacuum filtration of this suspension yielded 1.79 g (96%) of **16b** as a fine, white powder. The spectroscopic data for **16b** matched the literature values.[132]

Data for **16b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

6.87 – 6.80 (m, 2H), 6.69 – 6.63 (m, 2H), 3.62 (s, 2H), 1.33 (s, 9H).

Isomerization of 3-(Prop-1-en-1-yl)-1-tosyl-1*H*-indole (35b)



35a **35b**

A flame-dried, 50-mL Schlenk flask equipped with a Teflon stir bar and a rubber septum containing an argon atmosphere was charged with **35a** (682 mg, 2.19 mmol) and CH_2Cl_2 (10 mL). $PdCl_2(MeCN)_2$ (56 mg, 0.22 mmol, 0.10 equiv) was added in a single portion. The reaction mixture became wine red after a few min. The resulting homogenous reaction mixture was stirred at 23 °C for 12 h. The reaction mixture was then filtered over Celite, washed with CH_2Cl_2

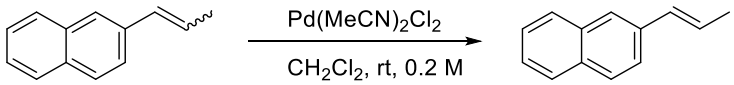
(2 x 10 mL), and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford **35b** as an off white solid (*E:Z*, 90:10). Recrystallization from boiling TBME (2 mL) provided 517 mg (75%) of **35b** as a white solid (*E:Z*, 96:4). A second recrystallization from boiling TMBE (1.5 mL) provided 402 mg (60%) of **35b** (*E:Z*, 99:1). The spectroscopic data for **35b** matched the literature values.[126]

Data for **35b:**

^{1}H NMR: (500 MHz, $CDCl_3$)

8.01 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.72 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.53 (s, 1H), 7.34 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.23 (d, *J* = 7.7 Hz, 2H), 6.52 – 6.42 (m, 1H), 6.32 (dq, *J* = 16.0, 6.5 Hz, 1H), 2.36 (s, 3H), 1.94 (dd, *J* = 6.6, 1.7 Hz, 3H).

Isomerization of 2-(Prop-1-en-1-yl)naphthalene (34b)



34a **34b**

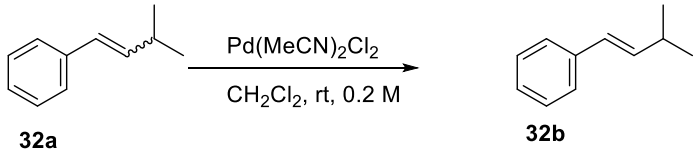
A flame-dried, 50-mL Schlenk flask equipped with a Teflon stir bar and a rubber septum containing an argon atmosphere was charged with **34a** (380 mg, 2.26 mmol) and CH_2Cl_2 (10 mL). $PdCl_2(MeCN)_2$ (58 mg, 0.22 mmol, 0.10 equiv) was added in a single portion. The reaction became wine red after a few min. The resulting homogenous reaction was stirred at 23 °C for 12 h. The reaction mixture was then filtered over Celite, washed with CH_2Cl_2 (2 x 10 mL), and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford **34b** as an off white solid (*E:Z*, 98:2). Recrystallization from boiling ethanol (3 mL) provided 323 mg (85%) of **34b** as a white solid (*E:Z*, 99:1).

Data for **34b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.84 – 7.73 (m, 3H), 7.70 – 7.64 (m, 1H), 7.57 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.43 (dddd, *J* = 17.7, 8.3, 6.9, 1.4 Hz, 2H), 6.57 (dd, *J* = 15.8, 1.8 Hz, 1H), 6.38 (dq, *J* = 15.7, 6.6 Hz, 1H), 1.95 (dd, *J* = 6.6, 1.7 Hz, 3H).

Isomerization of 2-(Prop-1-en-1-yl)naphthalene (32b)



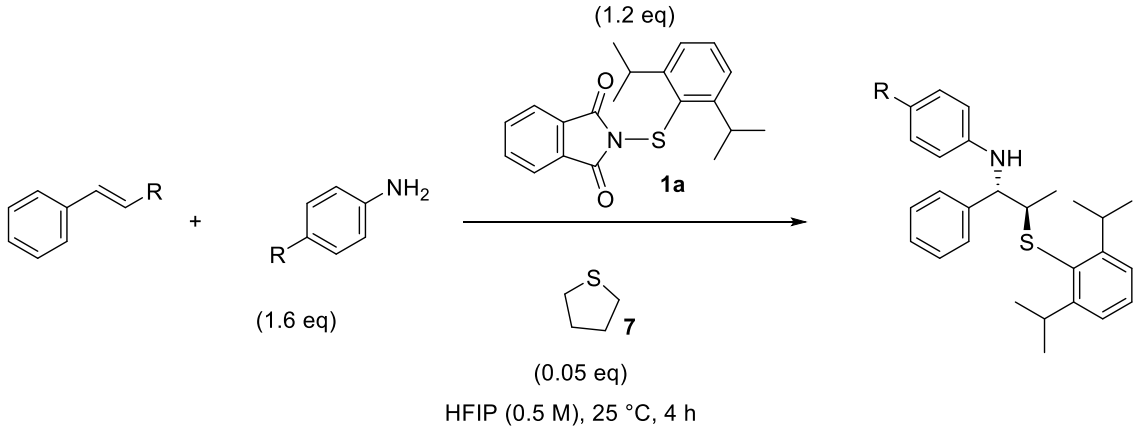
A flame-dried, 100-mL Schlenk flask equipped with a Teflon stir bar and a rubber septum containing an argon atmosphere was charged with **32a** (1.17 g, 8.0 mmol) and CH_2Cl_2 (40 mL). $PdCl_2(MeCN)_2$ (207 mg, 0.80 mmol, 0.10 equiv) was added in a single portion. The reaction became wine red after a few min. The resulting homogenous reaction was stirred at 23 °C for 12 h. The reaction mixture was then filtered over Celite, washed with CH_2Cl_2 (2 x 20 mL), and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford **32b** as an clear oil (*E:Z*, 99:1). Further purification via Kugelrohr distillation (90 °C, 0.2 mm Hg) provided 1.02 g (87%) of pure **32b** as a clear oil. The spectroscopic data for **32b** matched the literature values.

Data for **32b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.38 – 7.34 (m, 2H), 7.30 (td, *J* = 7.7, 1.9 Hz, 2H), 7.22 – 7.14 (m, 1H), 6.35 (dt, *J* = 16.0, 1.8 Hz, 1H), 6.20 (ddd, *J* = 15.9, 6.8, 2.0 Hz, 1H), 2.48 (dqd, *J* = 8.7, 6.8, 5.0 Hz, 1H), 1.10 (dd, *J* = 6.6, 2.2 Hz, 6H).

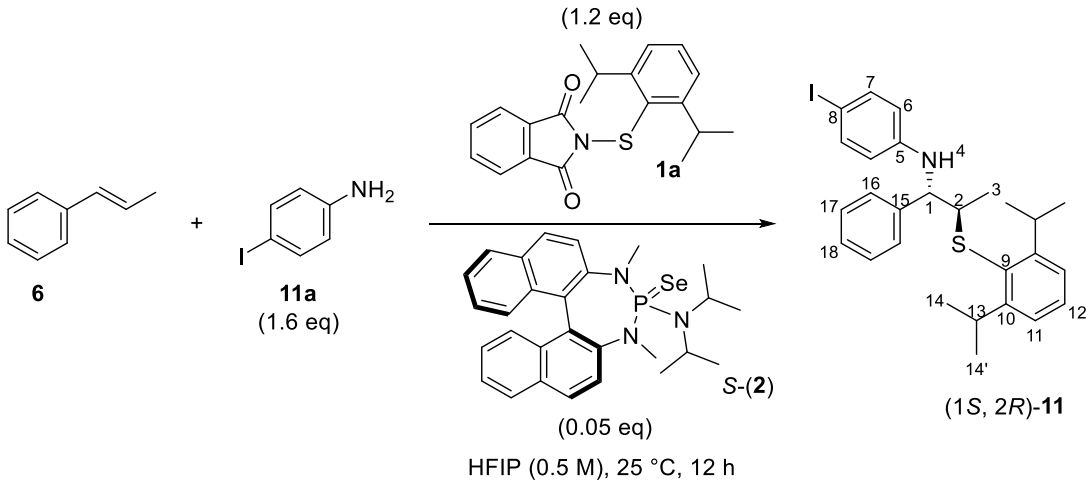
Preparation of Racemic Standards



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with olefin (1.0 equiv), hexafluoroisopropyl alcohol (0.5M), amine (1.60 equiv) and **1a** (1.20 equiv). A homogeneous, yellow solution resulted. Tetrahydrothiophene **7** (0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 4 h. Full conversion was observed by TLC. The

reaction mixture was diluted with EtOAc, decanted into a separatory funnel. The vial was rinsed with EtOAc and the reaction mixture further diluted with EtOAc and 50% brine. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with 50% brine, and were then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude racemic product. The product was purified by chromatography to afford the racemic product, generally as a foam.

Preparation of *N*-((1*R*,2*S*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-4-iodoaniline (11)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)*-2-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-iodoaniline **11a** (350 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**11**. The product was purified by chromatography (29 g silica gel, 2 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford 450 mg (85%) of (+)-**11** as an off-white foam. The

product was purified by trituration as follows. The crude material was suspended in pentane (2 mL) and sonicated at 23 °C and cooled to -20 °C for 2 h. Vacuum filtration of this suspension yielded 424 mg (80%) of analytically pure (+)-**11** as a fine, white powder.

Data for (+)-**11**:

m.p.: 100–102 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.38 – 7.27 (m, 5H, HC(18), HC(17) and HC(16)), 7.26 – 7.21 (m, 1H, HC(12)), 7.20-7.13 (m, 4H, HC(11) and HC(7)), 6.26 (d, J = 8.7 Hz, 2H, HC(6)), 4.57 (d, J = 3.3 Hz, 1H, HN(4)), 4.16 (t, J = 3.2 Hz, 1H, HC(1)), 3.80 (hept, J = 6.9 Hz, 2H, HC(13)), 3.23 (qd, J = 7.2, 3.2 Hz, 1H, HC(2)), 1.22 (d, J = 6.8 Hz, 6H, H_3C(14')), 1.17 (d, J = 7.1 Hz, 3H, H_3C(3)), 1.04 (d, J = 6.8 Hz, 6H, H_3C(14)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.6 (C(10)), 147.1 (C(15)), 140.4 (C(5)), 137.5 (HC(16)), 129.7 (C(9)), 129.5 (HC(18)), 128.6 (HC(17)), 127.3 (HC(12)), 126.8 (HC(7)), 123.7 (HC(11)), 116.3 (HC(6)), 78.6 (C(8)), 60.0 (HC(1)), 52.3 (HC(2)), 31.6 (HC(13)), 24.8 (H_3C(14')), 23.9 (H_3C(3)), 13.9 (H_3C(14)).

IR: (neat)

3356 (w), 2961 (m), 1592 (m), 1488 (s), 1459 (m), 1376 (w), 1360 (m), 1307 (m), 1288 (m), 1270 (s), 1184 (w), 1123 (m), 1050 (w), 1038 (m), 985 (w), 926 (w), 846 (w), 810 (s), 798 (s), 765 (m), 744 (s), 710 (s), 692 (m), 662 (m), 628 (w), 563 (w), 492 (m).

LRMS: (EI, 70 eV)

181.1 (10), 308.0 (100), 309.0 (15), 529.1.

TLC: R_f 0.49 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ +119.5 (c = 1.12, 100% EtOH)

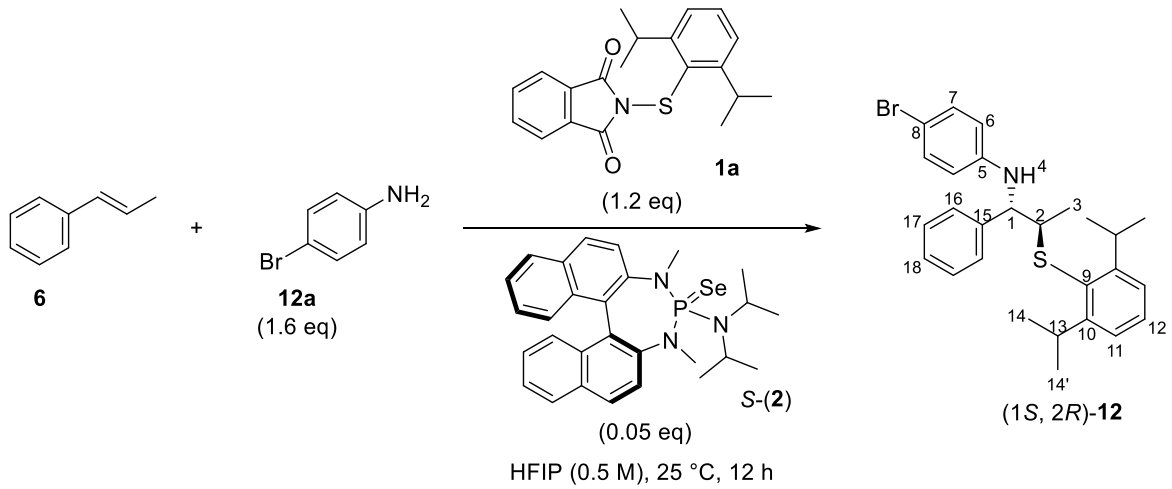
HPLC: t_R 10.7 min (1.6%); t_R 18.0 min (98.4%) (Chiralpak IB-3, hexanes/*i*-PrOH, 99.9:0.1, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{27}H_{33}INS$ (539.52)

Calcd: C, 61.24%; H, 6.09%; N, 2.65%

Found: C, 61.15%; H, 6.09%; N, 2.73%

Preparation of 4-Bromo-*N*-((1*S*,2*R*)-2-((2,6-diisopropylphenyl)thio)-1-phenylpropyl)aniline (12)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-bromoaniline **12a** (275 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). The reaction mixture was sonicated for 2 min to dissolve remaining solids to give a homogenous yellow solution. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. During the course of the reaction a white precipitate formed. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**12**. The product was purified by chromatography (31 g silica gel, 2 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford a thick, impure oil to which 1 ml of hexanes was added and sonicated at 23 °C which resulted in the precipitation of a white solid. Solvent was removed under reduced pressure (30 °C, 15 mm Hg) to afford 417 mg (87%) of (+)-**12**. Recrystallization from boiling hexanes provided 387 mg (80%) of analytically pure (+)-**12** as a fine, white powder.

Data for (+)-**12**:

m.p.: 100–102 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.36 (t, *J* = 7.7 Hz, 1H, HC(12)), 7.32 – 7.27 (m, 2H, HC(16)), 7.27 – 7.22 (m, 1H (HC(18)), 7.21 – 7.13 (m, 6H, (HC(7). HC(11), HC(17)), 6.35 (d, *J* = 8.8 Hz, 2H, HC(6)), 4.56 (d, *J* = 2.2 Hz, 1H, HN(4)), 4.16 (t, *J* = 3.0 Hz, 1H, HC(1)), 3.80 (hept, *J* = 6.9 Hz, 2H (HC(13)), 3.24 (qd, *J* = 7.2, 3.2 Hz, 1H, HC(1)), 1.22 (d, *J* = 6.8 Hz, 6H, H_3C(14')), 1.18 (d, *J* = 7.2 Hz, 3H, H_3C(3)), 1.05 (d, *J* = 6.8 Hz, 6H, H_3C(14)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.6 (C(10)), 146.6 (C(5)), 140.4 (C(15)), 131.7 (HC(7)), 129.8 (C(9)), 129.5 (HC(12)), 128.6 (HC(16)), 127.3 (HC(18)), 126.8 (HC(17)), 123.7 (HC(11)), 115.6 (HC(6)), 109.5 (C(8)), 60.1 (HC(1)), 52.3 (HC(2)), 31.6 (HC(13)), 24.8 (H_3C(14')), 23.9 (H_3C(14)), 13.9 (H_3C(3)).

IR: (neat)

3361 (w), 2961 (m), 1593 (m), 1490 (s), 1456 (m), 1376 (w), 1361 (m), 1306 (m), 1290 (m), 1272 (s), 1181 (w), 1122 (m), 1075 (w), 1050 (w), 1040 (m), 1000 (w), 927 (w), 813 (s), 798 (s), 765 (m), 744 (s), 711 (s), 671 (m), 559 (w), 488 (m), 460 (m).

LRMS: (EI, 70 eV)

95.1 (13), 97.1 (17), 117.1 (11), 129.1 (19), 149.0 (17), 256.2 (21), 260.0 (100), 262.0 (98), 261.0 (16), 446.1 (123).

TLC: R_f 0.49 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

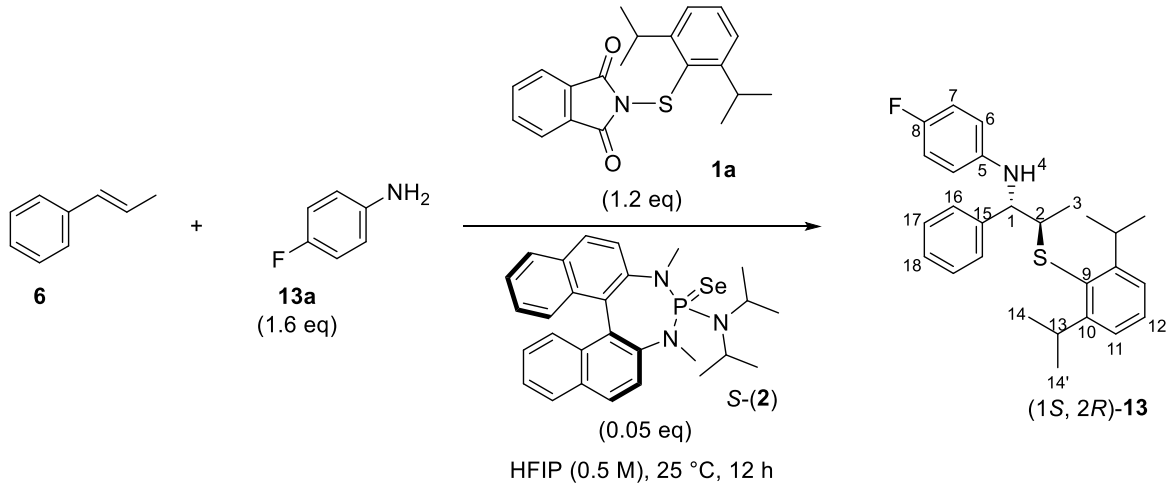
Opt. Rot.: $[\alpha]_D^{24}$ +119.1 (*c* = 1.03, 100% EtOH)

HPLC: t_R 10.32 min (1.7%); t_R 16.09 min (98.3%) (Chiralpak IB-3, hexanes/*i*-PrOH, 99.9:0.1, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{27}H_{32}BrNS$ (482.52)

Calcd:	C, 67.21%;	H, 6.68%;	N, 2.90%
Found:	C, 66.96%;	H, 6.66%;	N, 3.00%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-4-fluoroaniline (13)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-fluoroaniline **13a** (178 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**13**. The product was purified by chromatography (70 g silica gel, 2.5 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford 368 mg (87%) of (+)-**13** as a yellow-orange solid. The product was purified by trituration as follows. The crude material was suspended in methanol (2 mL) and sonicated at 23 °C and cooled to -20 °C for 2 h. Vacuum filtration of this suspension yielded 334 mg (79%) of analytically pure (+)-**13** as a fine, off white powder.

Data for (+)-**13**:

m.p.: 78–80 °C (methanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 (t, *J* = 7.7 Hz, 1H, HC(12)), 7.30 – 7.24 (m, 2H, HC(17)), 7.25 – 7.20 (m, 1H, HC(18)), 7.19 – 7.14 (m, 4H, HC(11) and HC(16)), 6.77 (t, *J* = 8.7 Hz, 2H, HC(7)), 6.38 (dd, *J* = 8.9, 4.3 Hz, 2H, HC(6)), 4.42 (d, *J* = 2.7 Hz, 1H, HN(4)), 4.10 (t, *J* = 2.9 Hz, 1H, HC(1)), 3.78 (hept, *J* = 6.9 Hz, 2H, HC(13)), 3.20 (qd, *J* = 7.2, 3.2 Hz, 1H, HC(2)), 1.19 (d, *J* = 7.0 Hz, 6H, HC(14')), 1.17 (d, *J* = 7.2 Hz, 3H, HC(3)), 1.01 (d, *J* = 6.9 Hz, 6H, HC(14)).

^{13}C NMR: (126 MHz, $CDCl_3$)

156.0 (d, *J* =235.1 Hz, 1C, C(8)), 153.6 (C(10)), 144.0 (d, *J*=1.8 Hz, 1C, C(5)), 140.9 (C(15)), 129.9 (HC(9)), 129.5 (HC(12)), 128.5 (HC(17)), 127.2 (HC(18)), 126.9 (HC(16)), 123.70 (HC(11), 115.36 (d, *J*=22.3 Hz, 1C, HC(7)), 114.7 (d, *J*=7.4 Hz, 1C, HC(6)), 60.5 (HC(1)), 52.6 (HC(2)), 31.6 (HC(13)), 24.8 (H_3C(14')), 23.9 (H_3C(14)), 13.8 (H_3C(3)).

^{19}F NMR: (470 MHz, $CDCl_3$)

-127.92 (tt, *J*= 8.3, 4.4 Hz).

IR: (neat)

2965 (m), 1505 (s), 1450 (m), 1377 (w), 1359 (w), 1313 (w), 1285 (w), 1218 (m), 1180 (w), 1154 (w), 1129 (w), 1103 (w), 1042 (w), 1031 (w), 988 (w), 923 (w), 815 (s), 807 (m), 781 (m), 749 (s), 704 (m), 693 (m), 630 (w), 593 (w), 512 (m), 496 (m), 469 (w).

LRMS: (EI, 70 eV)

91.1 (22), 111.0 (33), 115.1 (22), 117.1 (37), 118.1 (14), 149.0 (37), 177.1 (12), 191.1 (14), 200.1 (100), 201.1 (14), 219.1 (28).

TLC: R_f 0.37 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

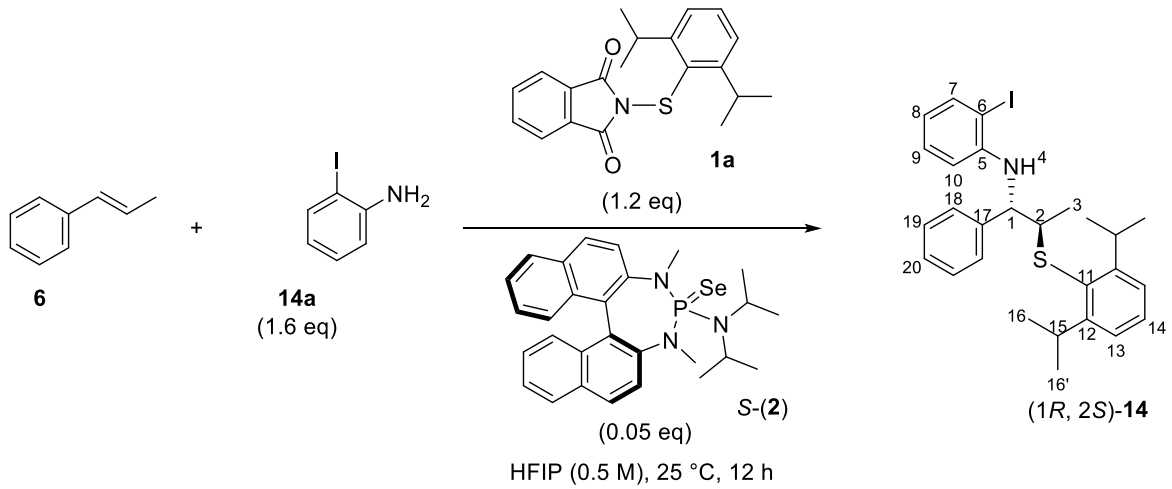
Opt. Rot.: $[\alpha]_D^{24}$ +84.8 (*c* = 1.10, $CHCl_3$)

HPLC: t_R 7.85 min (1.0%); t_R 10.6 min (99.0%) (Chiralpak IB-3, hexanes/*i*-PrOH, 99.9:0.1, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{27}H_{32}FNS$ (421.22)

Calcd: C,	76.92%;	H, 7.65%;	N, 3.32%
Found: C,	76.94%;	H, 7.69%;	N, 3.46%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-2-iodoaniline (14)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 2-iodoaniline **14a** (350 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). The reaction mixture was sonicated for 2 min to dissolve remaining solids to give a homogenous yellow solution. Catalyst (*S*)-**5** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 49:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**14**. The product was purified by chromatography (65 g silica gel, 3.5 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford an orange solid to which pentane (3 mL) was added and sonicated at 23 °C. The solution was concentrated under reduced pressure (30 °C, 15 mm Hg) to afford 458 mg (86%) of (+)-**14**. The product was purified by trituration as follows. The crude material was suspended in ethanol (2 mL) and sonicated at 23 °C and cooled to -20 °C for 2 h. Vacuum filtration of this suspension yielded 406 mg (76%) of analytically pure (+)-**14** as a fine, orange powder.

Data for (+)-**14**:

m.p.: 46–48 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.66 (dd, *J* = 7.8, 1.2 Hz, 1H, HC(10)), 7.28 (t, *J* = 7.7 Hz, 1H, HC(14)), 7.25 – 7.21 (m, 2H, HC(19)), 7.21 – 7.16 (m, 1H, HC(20)), 7.14 – 7.10 (m, 4H, HC(13) and HC(18)), 6.86 (t, *J* = 7.0 Hz, 1H, HC(8)), 6.35 (td, *J* = 7.6, 1.4 Hz, 1H, HC(9)), 5.94 (dd, *J* = 8.2, 1.4 Hz, 1H, HC(7)), 5.15 (d, *J* = 2.8 Hz, 1H, HN(4)), 4.12 (t, *J* = 3.0 Hz, 1H, HC(1)), 3.77 (hept, *J* = 7.0 Hz, 2H, HC(15)), 3.25 (qd, *J* = 7.1, 3.1 Hz, 1H, HC(2)), 1.23 – 1.15 (m, 9H, H_3C(3) and H_3C(16')), 0.94 (d, *J* = 6.3 Hz, 3H, H_3C(16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.9 (C(15)), 146.4 (C(5)), 140.3 (C(17)), 138.8 (HC(10)), 129.7 (C(11)), 129.5 (HC(14)), 129.1 (HC(8)), 128.6 (HC(19)), 127.3 (HC(20)), 126.9 (HC(18)), 123.7 (HC(13)), 119.0 (HC(9)), 112.5 (HC(7)), 86.3 (C(6)), 60.5 (HC(1)), 52.0 (HC(2)), 31.6 (HC(15)), 24.9 (H_3C(16')), 23.8 (H_3C(16)), 14.0 (H_3C(3)).

IR: (neat)

3350 (w), 3058 (w), 2961 (m), 2925 (w), 2865 (w), 1589 (m), 1500 (m), 1447 (m), 1424 (m), 1380 (w), 1360 (m), 1310 (m), 1272 (w), 1245 (w), 1193 (w), 1178 (w), 1133 (w), 1106 (w), 1069 (w), 1051 (m), 1037 (w), 1006 (m), 928 (w), 837 (w), 799 (m), 742 (s), 705 (s), 666 (m), 625 (w), 533 (w), 513 (w), 459 (w).

LRMS: (EI, 70 eV)

91.1 (16), 115.1 (10), 117.1 (18), 149.0 (12), 151.1 (10), 179.1 (10), 180.1 (34), 182.1 (34), 182.1 (20), 194.1 (12), 308.0 (100), 309.0 (42).

TLC: R_f 0.61 (silica gel, hexanes/EtOAc, 49:1, UV/CAM)

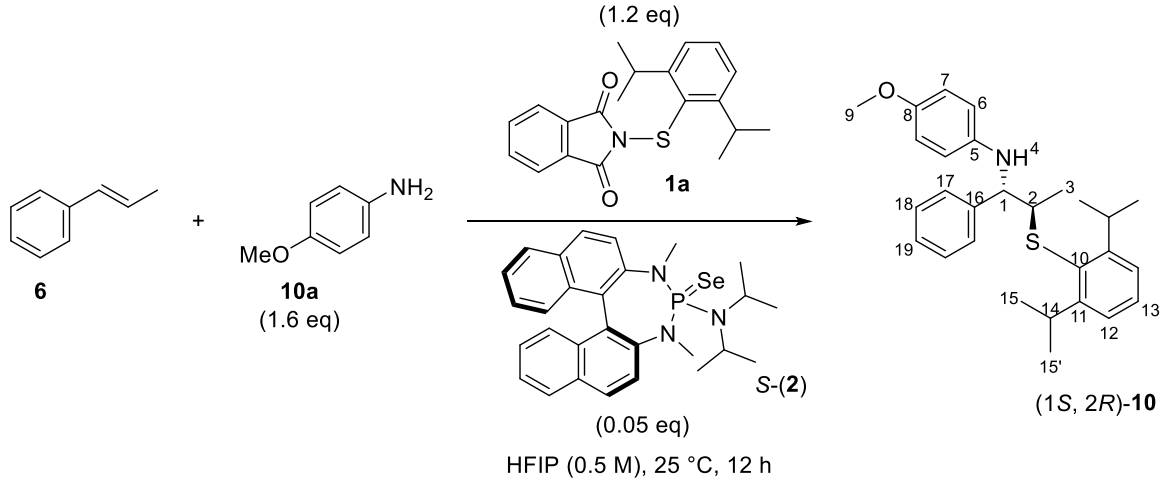
Opt. Rot.: $[\alpha]_D^{24}$ +69.4 (*c* = 1.14, $CHCl_3$)

HPLC: t_R 6.58 min (2.0%); t_R 7.38 min (98.0%) (Chiralpak IB-3, hexanes/*i*-PrOH, 99.9:0.1, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{27}H_{32}INS$ (529.52)

Calcd:	C, 61.24%;	H, 6.09%;	N, 2.65%
Found:	C, 61.17%;	H, 6.36%;	N, 2.78%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-4-methoxyaniline (10)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (E)-2-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-methoxyaniline **10a** (197 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The vial was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and were then dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**10**. The product was purified by chromatography (185 g grade III neutral alumina, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 376 mg (87%) of (+)-**10** as a white foam which would slowly turned red when in solution. Recrystallization from boiling hexanes (2 mL) provided 349 mg (81%) of analytically pure (+)-**10** as off-white crystals.

Data for (+)-**10**:

m.p.: 96–98 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 (t, *J* = 7.7 Hz, 1H, HC(13)), 7.30 – 7.25 (m, 2H, HC(17)), 7.23 – 7.18 (m, 3H, HC(18) and HC(19)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(12)), 6.68 – 6.64 (m, 2H, HC(7)), 6.43 – 6.39 (m, 2H, HC(6)), 4.30 (br s, 1H, NH(4)), 4.14 (d, *J* = 3.2 Hz, 1H, HC(1)), 3.80 (hept, *J* = 6.8 Hz, 2H, HC(14)), 3.69 (s, 3H, HC(9)), 3.21 (qd, *J* = 7.2, 3.2 Hz, 1H, HC(2)), 1.20 (d, *J* = 6.9 Hz, 6H, HC(15')), 1.16 (d, *J* = 7.2 Hz, 3H, HC(3)), 1.02 (d, *J* = 6.8 Hz, 6H, HC(15)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.7 (C(11)), 152.2 (C(8)), 141.9 (C(5)), 141.4 (C(16)), 130.1 (C(10)), 129.4 (HC(13)), 128.4 (HC(17)), 127.1 (HC(19)), 127.0 (HC(18)), 123.7 (HC(12)), 115.0 (HC(6)), 114.6 (HC(7)), 60.8 (HC(1)), 55.8 (HC(9)), 52.7 (HC(2)), 31.6 (HC(14)), 24.7 (HC(15')), 23.9 (HC(15)), 14.0 (HC(3)).

IR: (neat)

3358 (w), 2962 (w), 2830 (w), 1511 (s), 1464 (m), 1377 (w), 1359 (w), 1323 (w), 1271 (w), 1244 (s), 1182 (m), 1127 (w), 1044 (m), 1032 (m), 928 (w), 818 (s), 802 (m), 758 (m), 749 (m), 705 (s), 632 (w), 597 (w), 511 (m).

LRMS: (EI, 70 eV)

119.1 (49), 191.1 (38), 269.1 (23), 311.2 (100), 312.2 (27).

TLC: R_f 0.32 (silica gel, hexanes/EtOAc, 25:1, UV/CAM)

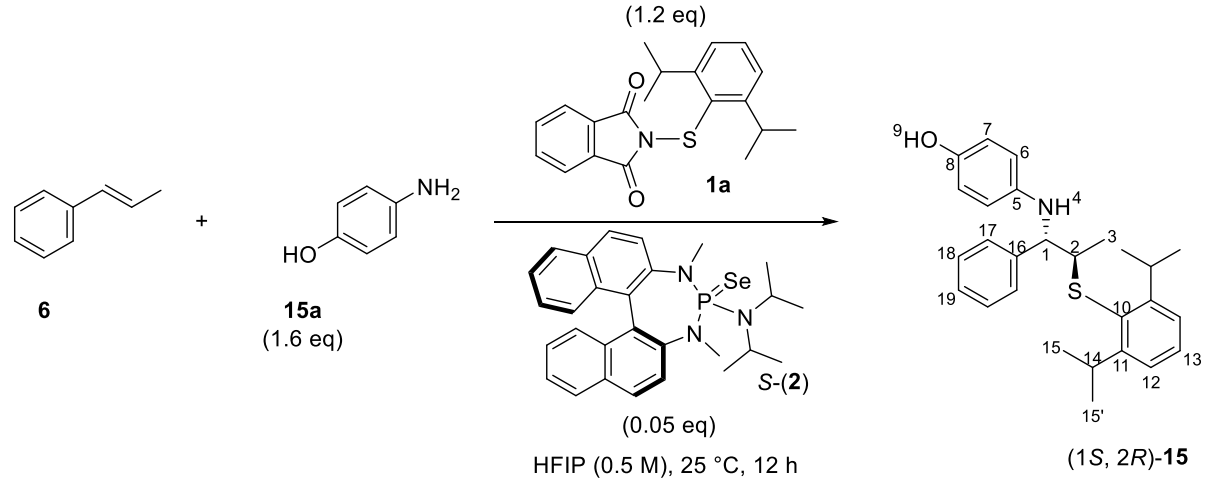
Opt. Rot.: $[\alpha]_D^{24}$ +93.7 (*c* = 1.13, 100% EtOH)

HPLC: t_R 7.58 min (3.6%); t_R 8.72 min (96.4%) (Chiralpak IB-3, hexanes/*i*-PrOH, 99.9:0.1, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{28}H_{35}NOS$ (433.65)

Calcd:	C,	77.55%;	H, 8.13%;	N, 3.23%
Found:	C,	77.59%;	H, 8.05%;	N, 3.39%

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)amino)phenol (15)



A 1 dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenol **15a** (175 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (4 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**15**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 24:1 (500 mL) to 97:3 (250 mL) to 9:1 (250 mL)) to afford 386 mg (92%) of (+)-**15** as an off white solid. The product was further purified by Kugelrohr distillation (140 °C, 3.4 x 10^{-5} mm Hg) to afford 369 mg (87%) of (+)-**15** as an air sensitive, light red solid.

Data for (+)-**15**:

m.p.: 64–66 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 (t, *J* = 7.7 Hz, 1H, HC(13)), 7.28 (d, *J* = 7.3 Hz, 2H, HC(18)), 7.23 – 7.15 (m, 5H, HC(12), HC(17) and HC(19)), 6.61 – 6.54 (m, 2H, HC(7)), 6.42 – 6.32 (m, 2H, HC(6)), 4.30 (s, 1H, NH(4)), 4.20 (s, 1H, HO(9)), 4.11 (d, *J* = 3.1 Hz, 1H, HC(1)), 3.80 (hept, *J* = 6.9 Hz, 2H, HC(14)), 3.20 (qd, *J* = 7.1, 3.0 Hz, 1H, HC(2)), 1.20 (d, *J* = 6.9 Hz, 6H, H_3C(15')), 1.16 (d, *J* = 7.2 Hz, 3H, H_3C(3)), 1.02 (d, *J* = 6.9 Hz, 6H, H_3C(15)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.8 (C(11)), 147.8 (C(8)), 142.1 (C(16)), 141.5 (C(5)), 130.2 (C(10)), 129.6 (HC(13)), 128.6 (HC(12)), 127.2 (HC(19)), 127.1 (HC(17)), 123.8 (HC(12)), 116.0 (HC(7)), 115.3 (HC(6)), 60.9 (HC(1)), 52.9 (HC(2)), 31.7 (HC(14)), 24.9 (H_3C(15')), 24.1 (H_3C(3)), 14.1 (H_3C(15)).

IR: (neat)

3363 (w), 2962 (m), 1512 (s), 1451 (m), 1361 (m), 1308 (w), 1237 (m), 1041 (m), 818 (m), 798 (m), 746 (s), 704 (s), 510 (m).

LRMS: (EI, 70 eV)

91.1 (16), 109.1 (12), 115.1 (16), 117.1 (29), 118.1 (14), 149.0 (25), 198.1 (100), 199.1 (13), 219.1 (16).

TLC: R_f 0.35 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

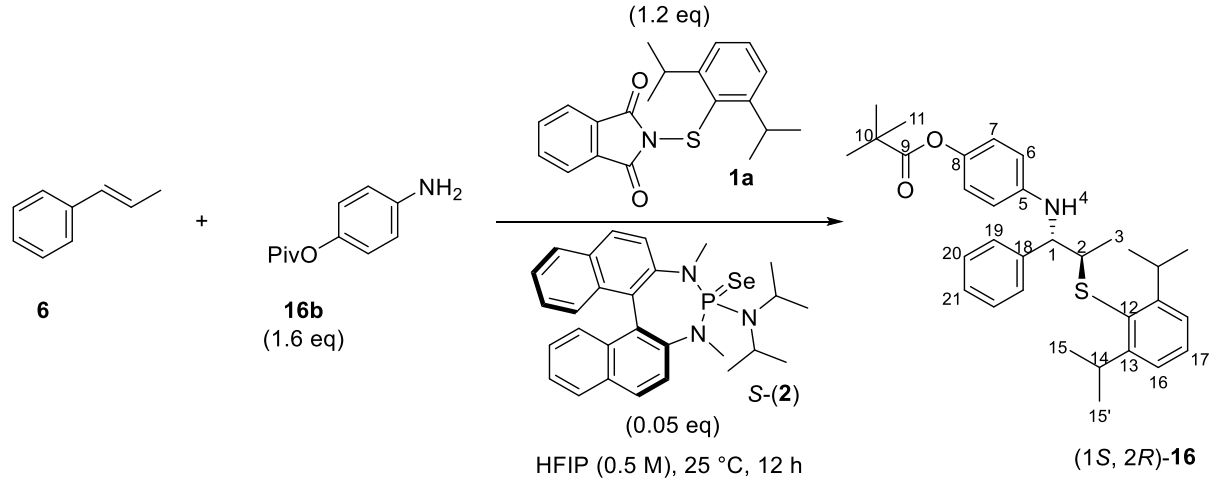
Opt. Rot.: $[\alpha]_D^{24}$ +79.5 (*c* = 1.42, $CHCl_3$)

HPLC: t_R 63.8 min (1.3%); t_R 68.7 min (98.6%) (Supelco Astec, hexanes/*i*-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{27}H_{33}NOS$ (518.76)

Calcd:	C, 77.28%;	H, 7.93%;	N, 3.34%
Found:	C, 77.46%;	H, 8.08%;	N, 3.50%

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)amino)phenyl Pivalate (16)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16b** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**16**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions,: hexanes/EtOAc gradient elution: 49:1 (250 mL) to 97:3 (100 mL) to 24:1 (100 mL)) to afford 452 mg (89%) of (+)-**16** as an off white solid. (+)-**16** was chromatographed again (2 cm column, 16 g silica gel, dry load on Celite, 10-mL fractions, hexanes/EtOAc (HPLC Grade), 97:3) to provide 423 mg (84%) of analytically pure (+)-**16** as an off white solid.

Data for (+)-**16**:

m.p.: 57–59 °C (hexanes/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.35 (t, *J* = 7.7 Hz, 1H, HC(17)), 7.33 – 7.27 (m, 2H, HC(20)), 7.26 – 7.22 (m, 1H, HC(21)), 7.22 – 7.16 (m, 4H, HC(19) and HC(16)), 6.76 (d, *J* = 8.8 Hz, 2H, HC(7)), 6.44 (d, *J* = 8.9 Hz, 2H, HC(6)), 4.52 (d, *J*=2.56 Hz, 1H, HN(4)), 4.18 (t, *J* = 2.9 Hz, 1H, HC(1)), 3.82 (hept, *J* = 7.0 Hz, 2H, HC(14)), 3.24 (qd, *J* = 7.2, 3.2 Hz, 1H, HC(2)), 1.33 (s, 9H, H_3C(11)), 1.22 (d, *J* = 6.8 Hz, 6H, H_3C(15)), 1.19 (d, *J* = 7.2 Hz, 3H, H_3C(3)), 1.06 (d, *J* = 6.8 Hz, 6H, H_3C(15')).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.6 (C(9)), 153.7 (C(13)), 145.3 (C(8)), 142.7 (C(5)), 140.8 (C(18)), 129.9 (C(12)), 129.5 (HC(17)), 128.5 (HC(20)), 127.2 (HC(21)), 126.9 (HC(19)), 123.7 (HC(16)), 121.7 (HC(7)), 114.3 (HC(6)), 60.4 (HC(1)), 52.5 (HC(2)), 38.9 (C(10)), 31.6 (HC(14)), 27.2 (CH_3(11)), 24.8 (H_3C(15')), 23.9 (H_3C(15)), 13.9 (H_3C(3)).

IR: (neat)

2963 (w), 1747 (m), 1612 (w), 1509 (s), 1480 (w), 1453 (m), 1362 (w), 1276 (m), 1197 (m), 1166 (m), 1118 (s), 1029 (m), 927 (w), 888 (w), 834 (w), 799 (m), 747 (m), 705 (m), 515 (m).

LRMS: (EI, 70 eV)

57.1 (24), 77.0 (19), 91.1 (24), 105.0 (37), 109.1 (51), 115.1 (20), 117.1 (36), 118.1 (14), 149.0 (74), 177.1 (11), 179.1 (14), 191.1 (12), 193.1 (13), 198.1 (13), 219.1 (26), 282.2 (100), 283.2 (20).

TLC: R_f 0.34 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

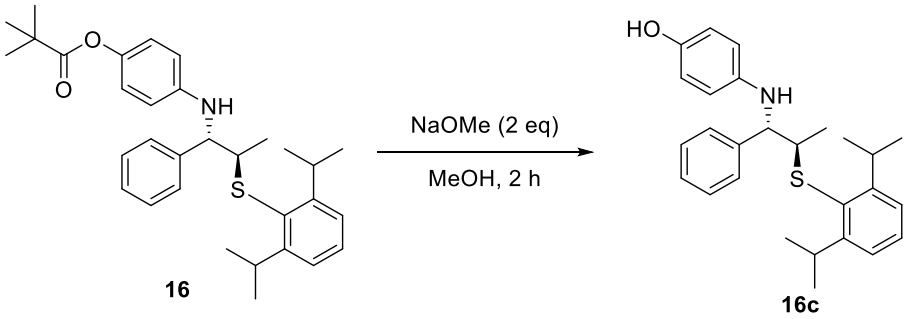
Opt. Rot.: $[\alpha]_D^{24}$ +69.0 (*c* = 1.12, $CHCl_3$)

HPLC: t_R 61.3 min (1.2%); t_R 65.5 min (98.8%) (Supelco Astec, hexanes/*i*PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C) [Determined with derivative (1*S*,2*R*)-**16c**]

Analysis: $C_{32}H_{41}NO_2S$ (518.76)

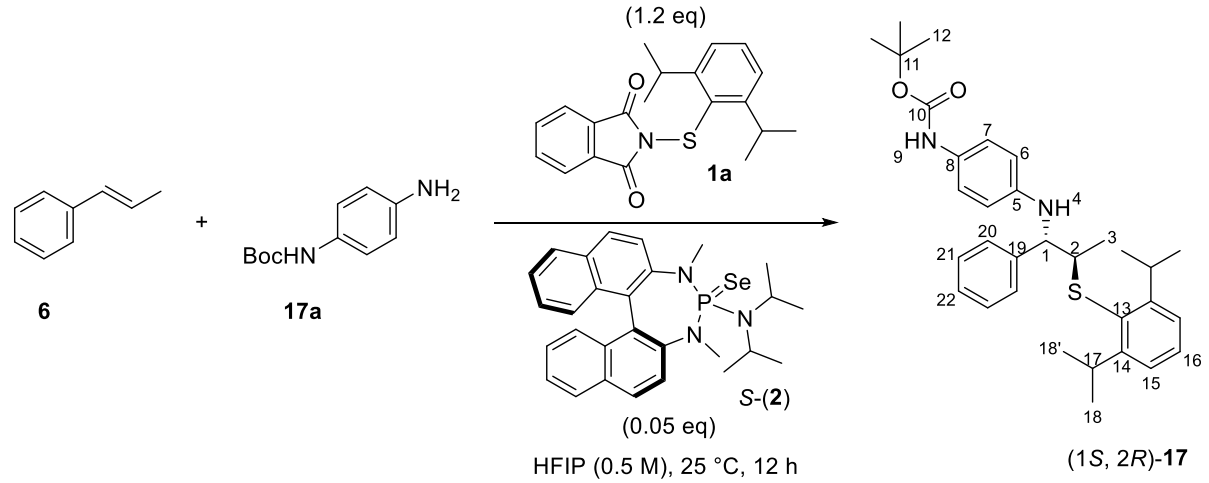
Calcd:	C, 76.30%;	H, 8.20%;	N, 2.78%
Found:	C, 76.18%;	H, 8.54%;	N, 2.94%

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)amino)phenol (16c)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with methanol (0.5 mL) and potassium (5 mg, 0.13 mmol, 2 equiv) and cooled to 0 °C in an ice/water bath. (1*S*, 2*R*)-**16** (32 mg, 0.064 mmol, 1.0 equiv) was charged resulting in a light tan suspension. The reaction was gradually warmed to 23 °C and stirred for 1 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture quenched with sat. aq. ammonium chloride solution (0.5 mL) and diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **16c**. The product was purified by passing through a pad of silica gel (0.5 g silica gel, 0.5 cm column, EtOAc) to afford 19 mg (71%) of **16c** as an off white solid. Spectra matched (1*S*, 2*R*)- **16c**.

Preparation of *tert*-Butyl (4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)amino)phenyl)carbamate (17)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), *tert*-butyl (4-aminophenyl)carbamate **17a** (333 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted after stirring. Catalyst (*S*)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**17**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution: 49:1 (100 mL) to 93:3 (200 mL) to 24:1 (200 mL)) to afford 453 mg (87%) of (+)-**17** as a tan foam. Analytically pure material was obtained by a second chromatography (2 cm column, 20 g silica gel, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc (HPLC Grade), 24:1) to provide 431 mg (83%) of analytically pure (+)-**17** as an off white foam.

Data for (+)-**17**:

m.p.: 68–70 °C (hexanes/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.34 (t, *J* = 7.7 Hz, 1H, HC(16)), 7.31 – 7.25 (m, 2H, HC(20)), 7.24 – 7.21 (m, 1H, HC(22)), 7.21 – 7.16 (m, 4H, HC(15) and HC(21)), 7.10 – 7.00 (m, 2H, HC(7)), 6.42 (d, *J* = 8.5 Hz, 2H, HC(6)), 6.18 (s, 1H, HN(9)), 4.44 (s, 1H, HN(4)), 4.19 (d, *J* = 3.2 Hz, 1H, HC(1)), 3.82 (hept, *J* = 6.9 Hz, 2H, HC(17)), 3.23 (qd, *J* = 7.1, 3.1 Hz, 1H, HC(2)), 1.50 (s, 9H, H_3C(12)), 1.21 (d, *J* = 6.8 Hz, 6H, H_3C(18)), 1.17 (d, *J* = 7.2 Hz, 3H, H_3C(3)), 1.04 (d, *J* = 6.8 Hz, 6H, H_3C(18)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.7 (C(10)), 153.2 (C(14)), 144.0 (C(8)), 141.0 (C(19)), 130.0 (HC(22)), 129.4 (HC(16)), 128.9 (C(13)), 128.5 (HC(20)), 127.1 (C(5)), 127.0 (HC(21)), 123.7 (HC(15)), 120.7 (HC(7)), 114.4 (HC(6)), 79.9 (C(11)), 60.4 (HC(1)), 52.5 (HC(2)), 31.6 (HC(17)), 28.4 (H_3C(12)), 24.7 (H_3C(18')), 24.0 (H_3C(18)), 14.0 (H_3C(3)).

IR: (neat)

2963 (w), 1704 (m), 1598 (w), 1517 (s), 1452 (m), 1404 (w), 1365 (m), 1306 (m), 1243 (m), 1224 (m), 1157 (s), 1052 (m), 1027 (m), 901 (w), 818 (m), 802 (m), 745 (m), 704 (m), 517 (m).

LRMS: (EI, 70 eV)

119.1 (22.6), 191.1 (18.9), 269.1 (12.9), 297.2 (16.0), 311.2 (100.0), 312.2 (30.1), 519.3 (34.7), 520.3 (12.2).

TLC: R_f 0.49 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

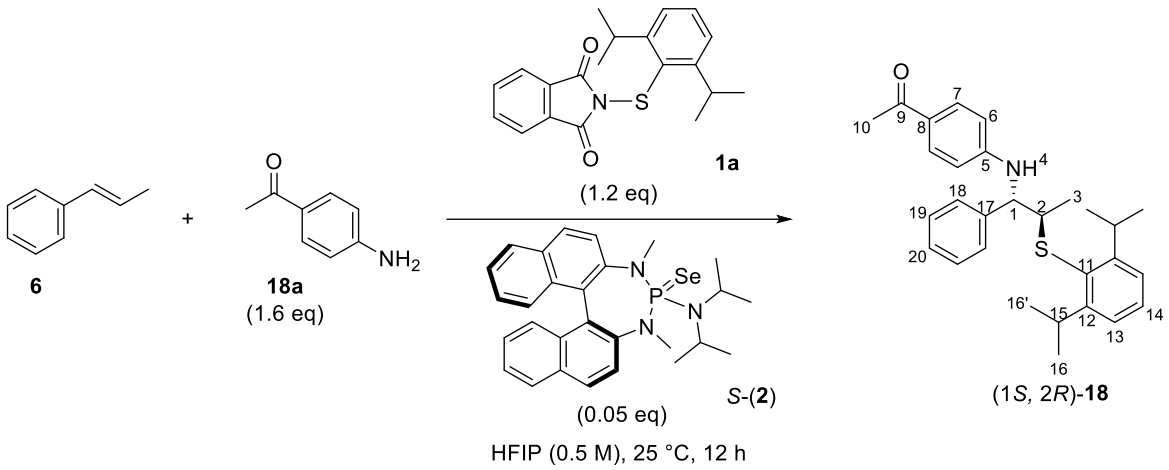
Opt. Rot.: $[\alpha]_D^{24}$ +96.3 (*c* = 1.02, 100% EtOH)

SFC: t_R 10.3 min (1.3%); t_R 11.5 min (98.7%) (Chiralpak OD, CO_2/MeOH, gradient 5% MeOH/CO_2 to 20% MeOH/CO_2 over 15 min, 220 nm, 24 °C)

Analysis: $C_{32}H_{42}N_2O_2S$ (518.76)

Calcd:	C, 74.09%;	H, 8.16%;	N, 5.40%
Found:	C, 73.77%;	H, 8.12%;	N, 5.19%

Preparation of 1-(4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)amino)phenyl)ethan-1-one (18)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 1-(4-aminophenyl)ethan-1-one **18a** (216 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**18** as a white solid. The product was purified by chromatography (65 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution: 9:1 (400 mL) to 5:1 (200 mL)) to afford 387 mg (87%) of (+)-**18** as a white solid. Recrystallization from boiling hexanes (4 mL) provided 330 mg (74 %) of analytically pure (+)-**18** as white crystals.

Data for (+)-**18**:

m.p.: 118-120 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.75 (d, *J* = 8.6 Hz, 2H, HC(7)), 7.37 (t, *J* = 7.7 Hz, 1H, HC(14)), 7.34 – 7.29 (m, 2H, HC(19)), 7.28 – 7.23 (m, 1H, HC(20)), 7.23 – 7.11 (m, 4H, HC(18) and HC(13)), 6.47 (d, *J* = 8.7 Hz, 2H, HC(6)), 5.02 (br s, 1H, HN(4)), 4.31 (t, *J* = 3.5 Hz, 1H, HC(1)), 3.81 (hept, *J* = 6.9 Hz, 2H, HC(15)), 3.28 (qd, *J* = 7.2, 3.3 Hz, 1H, HC(2)), 2.48 (s, 3H, H_3C(10)), 1.26 – 1.15 (m, 9H, H_3C(16') and H_3C(3)), 1.04 (d, *J* = 6.8 Hz, 6H, H_3C(16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

196.4 (C(9)), 153.6 (C(12)), 151.5 (C(8)), 139.9 (C(17)), 130.4 (HC(7)), 129.6 (HC(14)), 129.5 (C(11)), 128.7 (HC(19)), 127.5 (HC(20)), 127.3 (C(5)), 126.7 (HC(18)), 123.8 (HC(13)), 112.9 (HC(6)), 59.6 (HC(1)), 51.9 (HC(2)), 31.6 (HC(15)), 26.0 (H_3C(10)), 24.8 (H_3C(16')), 23.9 (H_3C(16)), 14.0 (H_3C(3)).

IR: (neat)

3403 (w), 2960 (m), 2861 (w), 1658 (s), 1597 (s), 1578 (s), 1519 (m), 1491 (w), 1452 (m), 1416 (m), 1381 (m), 1360 (m), 1333 (m), 1270 (s), 1185 (s), 1172 (m), 1129 (m), 1041 (m), 954 (m), 828 (m), 801 (m), 759 (m), 750 (m), 705 (s), 627 (w), 603 (m), 591 (m), 551 (m), 494 (m), 464 (w).

LRMS: (EI, 70 eV)

77.0 (34), 91.1 (25), 92.1 (12), 105.0 (69), 115.1 (19), 117.1 (33), 118.1 (13), 120.0 (25), 135.1 (13), 149.1 (93), 177.1 (11), 179.1 (14), 191.1 (10), 219.1 (20), 224.1 (100), 225.1 (17).

TLC: R_f 0.41 (silica gel, hexanes/EtOAc, 4:1, UV/CAM)

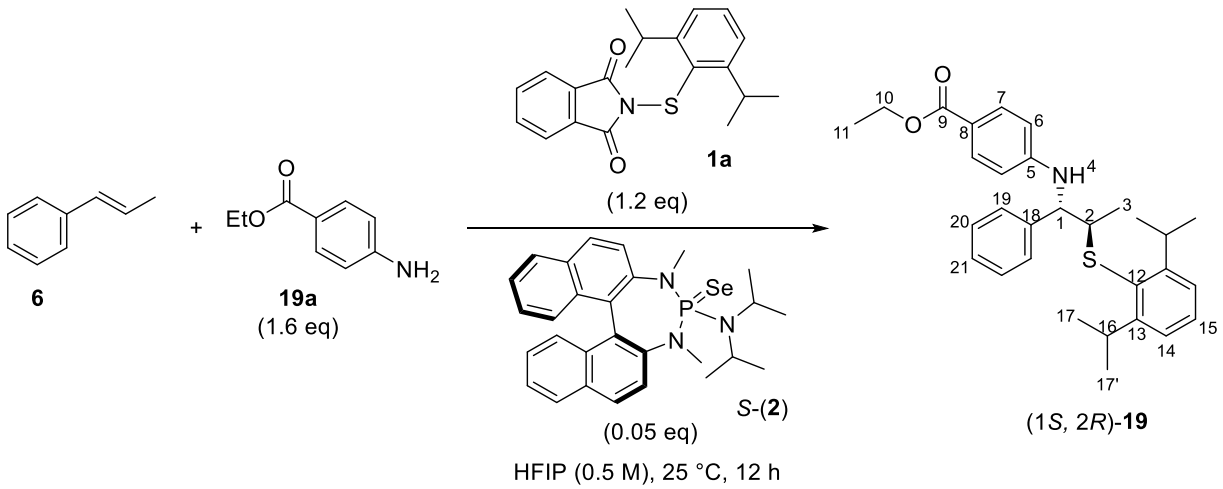
Opt. Rot.: $[\alpha]_D^{24}$ +185.5 (*c* = 1.27, $CHCl_3$)

HPLC: t_R 3.98 min (2.3%); t_R 4.6 min (97.7%) (Supelco Astec, hexanes/*i*PrOH, 60:40, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{29}H_{35}NOS$ (445.24)

Calcd:	C, 78.16%;	H, 7.92%;	N, 3.14%
Found:	C, 78.27%;	H, 8.17%;	N, 3.26%

Preparation of Ethyl 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)amino)benzoate (19)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), ethyl 4-aminobenzoate **19a** (264 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (5 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**19** as a white soild. The product was purified by chromatography (66 g silica gel, 3.5 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 19:1) to afford 405 mg (85%) of impure (+)-**19** as a white solid contaminated with **1a**. Recrystallization from boiling hexanes (5 mL) provided 355 mg (80%) of material that was contaminated with **1a**. A second recrystallization from boiling hexanes (4 mL) afforded 334 mg (70%) of analytically pure (+)-**19** as white needles.

Data for (+)-**19**:

m.p.: 137-139 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.79 (d, *J* = 8.7 Hz, 2H, HC(7))), 7.36 (t, *J* = 7.7 Hz, 1H, (HC(15)), 7.34 – 7.28 (m, 2H, (HC(20)), 7.28 – 7.23 (m, 1H, (HC(21)), 7.21 – 7.14 (m, 4H, HC(19) and HC(14)), 6.45 (d, *J* = 8.7 Hz, 2H, HC(6)), 4.93 (d, *J* = 3.6 Hz, 1H, HN(4)), 4.37 – 4.24 (m, 3H, H_2C(10) and HC(1)), 3.81 (hept, *J* = 6.9 Hz, 2H, HC(16)), 3.27 (qd, *J* = 7.2, 3.3 Hz, 1H, HC(2)), 1.35 (t, *J* = 7.1 Hz, 3H, H_3C(11)), 1.25 – 1.18 (m, 9H, H_3C(11) and H_3C(17')), 1.04 (d, *J* = 6.9 Hz, 6H, H_3C(17)).

^{13}C NMR: (126 MHz, $CDCl_3$)

166.8 (C(9)), 153.7 (C(13)), 151.2 (C(8)), 140.0 (C(18)), 131.2 (HC(7)), 129.6 (HC(15)), 129.6 (C(12)), 128.6 (HC(20)), 127.4 (HC(21)), 126.7 (HC(19)), 123.8 (HC(14)), 119.4 (C(5)), 112.9 (HC(6)), 60.2 (H_2C(10)), 59.6 (HC(1)), 52.0 (HC(2)), 31.6 (H_3C(16)), 24.8 (H_3C(17')), 24.0 (H_3C(17)), 14.4 (H_3C(11)), 13.9 (H_3C(3)).

IR: (neat)

3401 (w), 3056 (w), 2963 (m), 1729 (w), 1682 (s), 1605 (s), 1524 (s), 1503 (w), 1459 (m), 1448 (m), 1419 (w), 1384 (w), 1364 (m), 1342 (m), 1310 (m), 1272 (s), 1172 (s), 1131 (m), 1106 (m), 1093 (m), 1046 (m), 1024 (m), 996 (w), 929 (w), 897 (w), 880 (w), 840 (m), 798 (m), 772 (s), 747 (s), 705 (s), 674 (w), 644 (w), 618 (w), 568 (m), 508 (m), 481 (m).

LRMS: (EI, 70 eV)

77.0 (18), 91.1 (18), 92.1 (11), 105.0 (39), 115.1 (16), 117.1 (33), 118.1 (13), 120.0 (42), 137.0 (15), 149.0 (61), 165.1 (18), 219.1 (19), 226.1 (14), 254.1 (100), 255.1 (18).

TLC: R_f 0.51 (silica gel, hexanes/EtOAc, 4:1, UV/CAM)

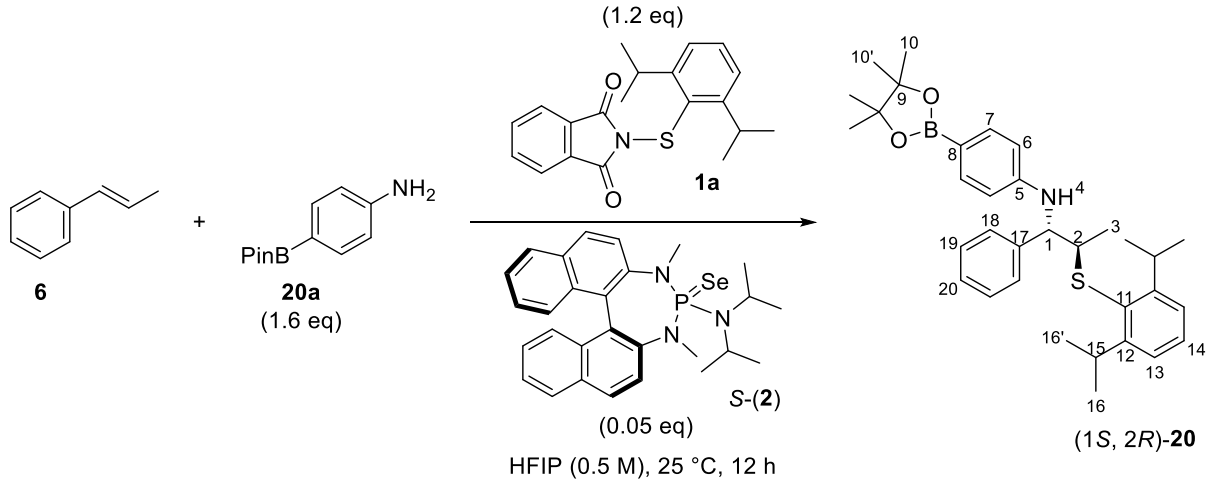
Opt. Rot.: $[\alpha]_D^{24}$ +181.2 (*c* = 1.21in $CHCl_3$)

HPLC: t_R 9.9 min (1.3%); t_R 11.1 min (98.7%) (Supelco Astec, hexanes/*i*PrOH, 95:5, 0.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{30}H_{37}NO_2S$ (475.25)

Calcd:	C, 75.75%;	H, 7.84%;	N, 2.94%
Found:	C, 75.61%;	H, 8.18%;	N, 3.18%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (20)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **20a** (351 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**5** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (4 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**20**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 462 mg (87%) of (+)-**20** as a white foam. Recrystallization from boiling hexanes provided 436 mg (82 %) of analytically pure (+)-**20** as white crystals.

Data for (+)-**20**:

m.p.: 144–146 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.54 (d, *J* = 7.9 Hz, 2H, HC(7)), 7.35 (t, *J* = 7.7 Hz, 1H, HC(14)), 7.30 – 7.25 (m, 2H, HC(19)), 7.25 – 7.20 (m, 1H, (HC(20)), 7.21 – 7.14 (m, 4H, HC(13) and HC(18)), 6.46 (d, *J* = 7.9 Hz, 2H, HC(6)), 4.72 (d, *J* = 3.3 Hz, 1H, HN(4)), 4.32 (t, *J* = 3.4 Hz, 1H, HC(1)), 3.84 (hept, *J* = 6.8 Hz, 2H, HC(15)), 3.26 (qd, *J* = 7.1, 3.3 Hz, 1H, HC(2)), 1.32 (s, 6H, H_3C(10')), 1.31 (s, 6H, H_3C(10)), 1.22 (d, *J* = 6.8 Hz, 6H, H_3C(16')), 1.18 (d, *J* = 7.1 Hz, 3H, H_3C(3)), 1.05 (d, *J* = 6.8 Hz, 6H, H_3C(16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.9 (C(15)), 150.1 (C(5)), 140.8 (C(17)), 136.2 (HC(7)), 130.0 (C(11)), 129.6 (HC(19)), 128.6 (HC(19)), 127.3 HC(18)), 127.0 (HC(13)), 123.9 (HC(20)), 113.3 (HC(6)), 83.3 (C(9)), 59.8 (HC(1)), 52.3 (HC(2)), 31.7 (HC(15)), 25.1 (H_3C(10')), 24.9 (H_3C(10)), 24.9 (H_3C(16')), 24.2 (H_3C(3)), 14.3 (H_3C(16)).

^{11}B NMR: (128 MHz, $CDCl_3$)

32.49 (br, (BC(8))

IR: (neat)

2958 (w), 1604 (s), 1469 (m), 1396 (m), 1353 (s), 1313 (s), 1271 (m), 1187 (m), 1142 (s), 1090 (m), 1046 (m), 962 (m), 860 (m), 816 (m), 800 (m), 761 (m), 749 (m), 710 (s), 673 (m), 657 (s), 511 (m).

LRMS: (EI, 70 eV)

220.2 (17.7), 308.2 (40.4), 522.2 (22.7), 523.2 (10.7), 529.3 (20.2), 530.3 (100.0), 531.3 (27.0), 532.3 (10.2), 536.2 (17.3), 538.2 (31.9), 582.1 (15.4), 584.1 (15.7), 586.1 (17.7).

TLC: R_f 0.38 (silica gel, hexanes/EtOAc, 23:2, UV/CAM)

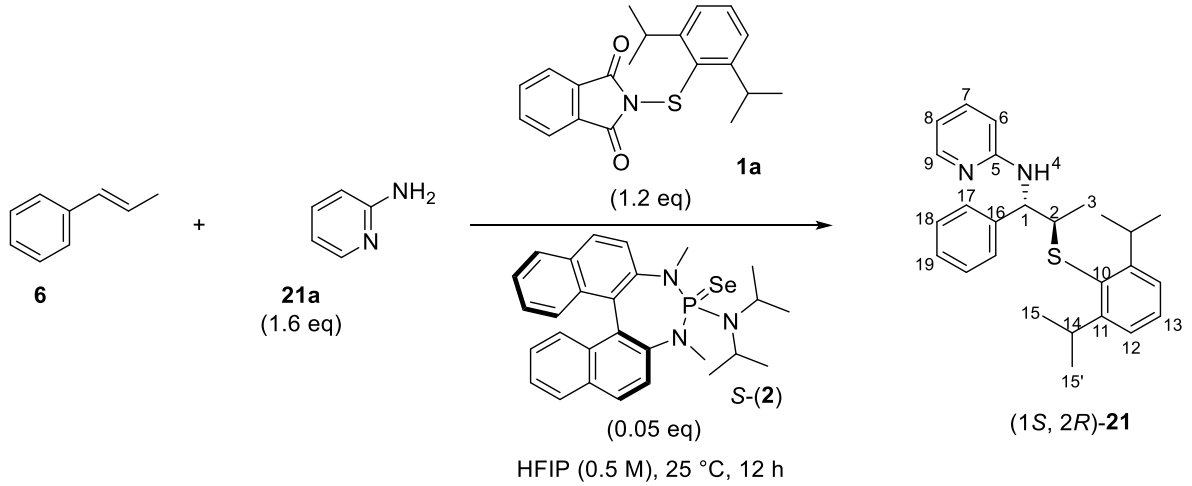
Opt. Rot.: $[\alpha]_D^{24}$ +110.1 (*c* = 0.92, 100% EtOH)

SFC: t_R 13.9 min (4.3%); t_R 14.7 min (95.7%) (Chiralpak OD, CO_2/MeOH, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 (10 min); isocratic 10% MeOH/CO_2 (10 min), 2.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{29}H_{35}NOS$ (445.24)

Calcd:	C, 74.84%;	H, 8.37%;	N, 2.64%
Found:	C, 74.77%;	H, 8.32%;	N, 2.95%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)pyridin-2-amine (21)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 2-aminopyridine **21a** (151 mg, 1.60 mmol, 1.60 equiv) and **1a** (407. mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (4 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**21**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 421 mg (>100%) of impure (+)-**21** as a tan foam. The residue was chromatographed a second time (25 g silica gel, 2 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford 357 mg (88%) of (+)-**21** as a white foam. Further purification via Kugelrohr distillation (130 °C, 3.5 x 10^{-5} mm Hg) provided 327 mg (81%) of analytically pure (+)-**21** as an off white solid.

Data for (+)-**21**:

m.p.: 54–56 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

8.14 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H, HC(9)), 7.38 – 7.27 (m, 4H, HC(13), HC(19) and HC(17)), 7.29 – 7.20 (m, 4H, HC(7) and HC(18)), 7.17 (d, *J* = 7.7 Hz, 2H, HC(12)), 6.59 (ddd, *J* = 7.1, 4.9, 0.8 Hz, 1H, HC(8)), 6.00 (d, *J* = 8.4 Hz, 1H, HC(6)), 5.39 (d, *J* = 4.6 Hz, 1H, HN(4)), 4.46 (t, *J* = 4.1 Hz, 1H, HC(1)), 3.86 (hept, *J* = 6.9 Hz, 2H, HC(14)), 3.28 (qd, *J* = 7.1, 3.5 Hz, 1H, HC(2)), 1.25 – 1.16 (m, 9H, H_3C(15') and H_3C(3)), 1.04 (d, *J* = 6.9 Hz, 6H, H_3C(15)).

^{13}C NMR: (126 MHz, $CDCl_3$)

158.4 (C(5)), 153.7 (C(14)), 148.3 (HC(9)), 140.6 (C(16)), 137.4 (HC(7)), 129.9 (C(10)), 129.4 (HC(13)), 128.5 (HC(17)), 127.3 (HC(19)), 126.8 (HC(18)), 123.6 (HC(12)), 113.5 (HC(8)), 106.9 (HC(6)), 58.8 (HC(1)), 51.8 (HC(2)), 31.5 (HC(14)), 24.7 (H_3C(15')), 23.9 (H_3C(15)), 14.1 (H_3C(3)).

IR: (neat)

2961 (m), 2925 (w), 2866 (w), 1597 (s), 1572 (m), 1498 (s), 1481 (s), 1444 (s), 1419 (m), 1381 (m), 1361 (m), 1330 (m), 1285 (m), 1245 (w), 1178 (w), 1153 (m), 1086 (w), 1052 (m), 983 (m), 928 (w), 801 (m), 770 (s), 746 (s), 702 (s), 619 (m), 536 (m), 512 (m).

LRMS: (EI, 70 eV)

77.0 (18), 78.0 (24), 91.1 (31), 105.0 (27), 115.1 (31), 116.1 (10), 117.1 (34), 118.1 (13), 123.0 (17), 128.1 (12), 134.0 (12), 135.0 (19), 137.0 (18), 149.0 (78), 151.1 (43), 177.1 (15), 179.1 (28), 183.1 (100), 184.1 (13), 192.1 (20), 193.1 (26), 194.1 (26), 219.1 (20), 310.2 (16), 386.2 (20).

TLC: R_f 0.51 (silica gel, hexanes/EtOAc, 4:1, UV)

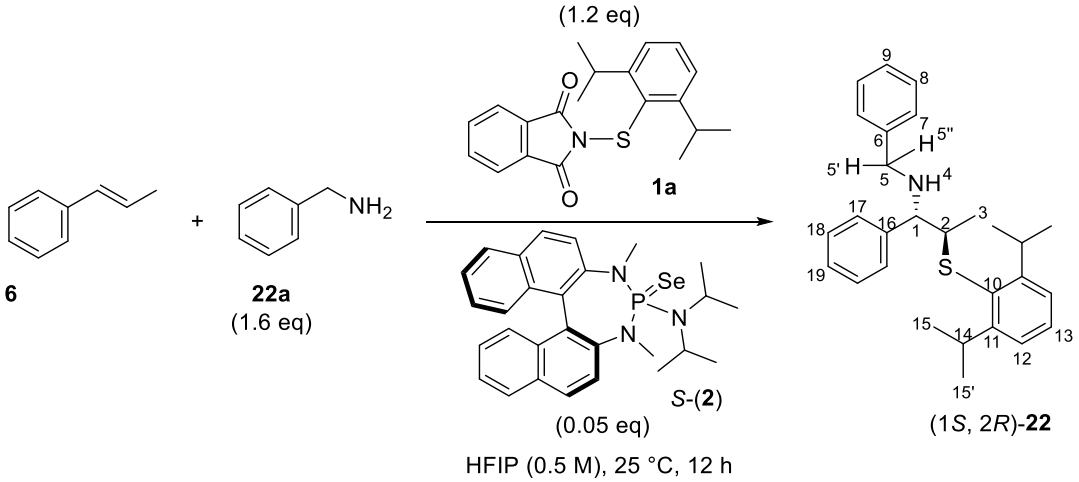
Opt. Rot.: $[\alpha]_D^{24}$ +53.5 (*c* = 1.13, $CHCl_3$)

HPLC: t_R 2.1 min (4.8 %); t_R 2.7 min (95.1%) (Chiralpak IB-3, hexanes/*i*-PrOH, 99:1, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{26}H_{32}N_2S$ (404.61)

Calcd:	C, 77.18%;	H, 7.97%;	N, 6.92%
Found:	C, 77.13%;	H, 8.24%;	N, 6.97%

Preparation of (1*S*,2*R*)-*N*-Benzyl-2-((2,6-diisopropylphenyl)thio)-1-phenylpropan-1-amine (22)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), benzylamine **22a** (171 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 24:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (5 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**22**. The product was purified by chromatography (63 g silica gel, 3.5 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 19:1) to afford 313 mg (74%) of (+)-**22** as a white foam. The product was purified by trituration as follows. The crude material was suspended in ethanol (2 mL) and sonicated at 23 °C and cooled to -20 °C for 12 h. Vacuum filtration of this suspension yielded 293 mg (70%) of analytically pure (+)-**22** as a fine, white powder.

Data for (+)-**22**:

m.p.: 73–75 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.42 – 7.38 (m, 2H, HC(aryl)), 7.38 – 7.31 (m, 7H, HC(aryl)), 7.31 – 7.27 (m, 1H, HC(aryl)), 7.27 – 7.23 (m, 1H, HC(aryl)), 7.19 (d, *J* = 7.7 Hz, 2H, HC(12)), 3.87 (h, *J* = 6.9 Hz, 2H, HC(14)), 3.83 (d, *J* = 3.5 Hz, 1H, HC(1)), 3.70 (d, *J* = 13.1 Hz, 1H, $H_2C(5'')$), 3.56 (d, *J* = 13.1 Hz, 1H, $H_2C(5')$), 3.08 (qd, *J* = 7.0, 3.3 Hz, 1H, HC(2)), 2.09 (s, 1H, HN(4)), 1.24 (d, *J* = 6.9 Hz, 6H, $H_3C(15')$), 1.20 (d, *J* = 6.8 Hz, 6H, $H_3C(15)$), 1.13 (d, *J* = 7.1 Hz, 3H, $H_3C(3)$).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.7 (C(11)), 141.7 (C(16)), 140.9 (C(6)), 130.9 (C(10)), 129.3 (HC(aryl)), 128.5 (HC(aryl)), 128.4 (HC(aryl)), 128.2 (HC(aryl)), 127.9 (HC(aryl)), 127.3 (HC(7)), 127.0 (HC(17)), 123.7 (HC(aryl)), 65.4 (HC(12)), 53.3 (HC(1)), 52.1 (HC(2)), 31.7 (HC(14)), 24.64 ($H_3C(15')$), 24.58 ($H_3C(15)$), 14.7 ($H_3C(3)$).

IR: (neat)

2957 (m), 2836 (w), 1572 (w), 1491 (w), 1451 (m), 1380 (w), 1359 (w), 1213 (w), 1192 (w), 1177 (w), 1131 (w), 1077 (m), 1052 (w), 1028 (w), 998 (w), 951 (w), 929 (w), 840 (w), 804 (m), 753 (s), 731 (m), 711 (m), 701 (s), 637 (w), 594 (w), 524 (w), 506 (m), 488 (w), 459 (w).

LRMS: (EI, 70 eV)

117.1 (12.1), 149.0 (15.4), 196.1 (100.0), 197.1 (83.8).

TLC: R_f 0.36 (silica gel, hexanes/EtOAc, 24:1, UV)

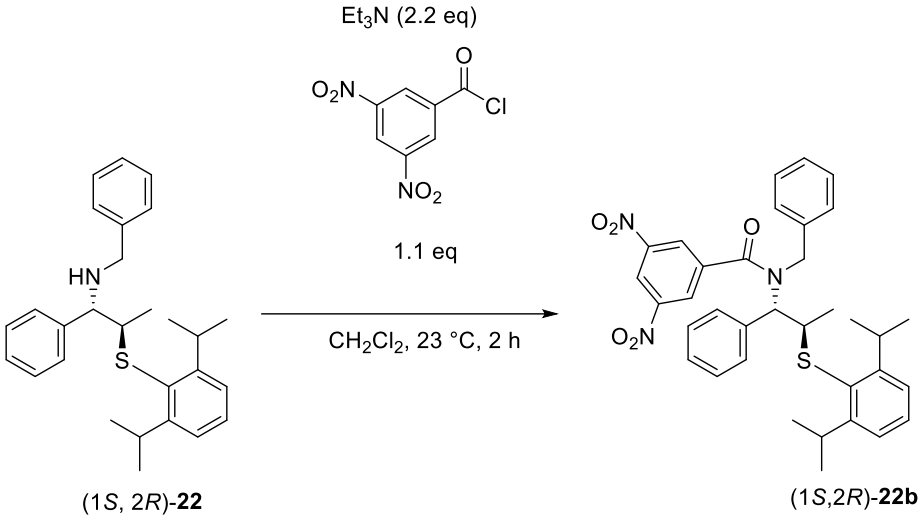
Opt. Rot.: $[\alpha]_D^{24}$ +41.0 (*c* = 1.13, $CHCl_3$)

SFC: t_R 15.4 min (1.4%); t_R 20.1 min (98.6%) (Chiralpak OD, CO_2/MeOH, gradient 5% MeOH/CO_2 to 20% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C) [Determined with (1*S*,2*R*)- **22b**]

Analysis: $C_{28}H_{35}NS$ (417.65)

Calcd:	C, 80.52%;	H, 8.45%;	N, 3.35%
Found:	C, 80.31%;	H, 8.52%;	N, 3.58%

Preparation of *N*-Benzyl-*N*-((1*S*,2*R*)-2-((2,6-diisopropylphenyl)thio)-1-phenylpropyl)-3,5-dinitrobenzamide (22b)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**22** (15.0 mg, 0.035 mmol, 1.0 equiv), CH_2Cl_2 (300 μL), Et_3N (11 μL, 0.08 mmol, 2.2 equiv) and 3,5-dinitrobenzoyl chloride (9 mg, 0.04 mmol, 1.1 equiv) and the mixture was stirred at 23 °C for 2 h. A homogeneous, yellow solution resulted which slowly formed a precipitate over the course of the reaction. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **22b**. The product was purified by chromatography (7 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 18 mg (81%) of **22b** as a white solid.

Data for **22b**:

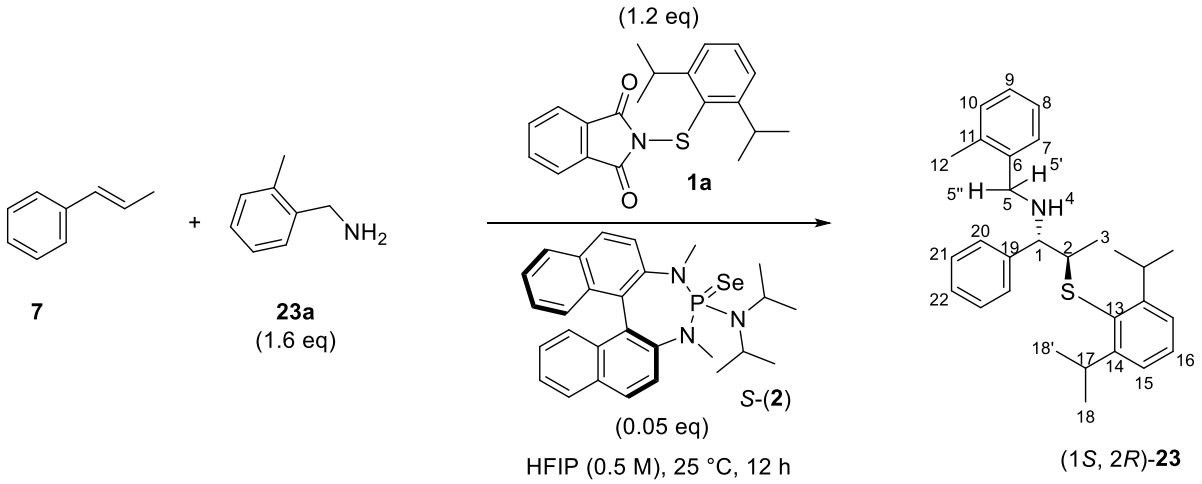
^{1}H NMR: (500 MHz, DMSO-d_6, 80 °C)

8.73 (br s, 1H), 8.22 (br s, 2H), 7.58 (br s, 2H), 7.43 – 7.34 (m, 3H), 7.31 (t, J = 7.7 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 7.02 (br s, 3H), 6.60 (br s, 2H), 5.39 (br s, 1H), 4.63 (d, J = 16.7 Hz, 1H), 4.50 (d, J = 16.6 Hz, 1H), 4.07 (br s, 1H), 3.70 (br s, 2H), 1.25 (s, 3H), 1.10 (d, J = 6.5 Hz, 12H).

HRMS: (EI, 70 eV)

Calcd for $C_{35}H_{37}N_3O_5S$ ([M]$^+$): 612.2532, Found: 612.2527

Preparation of (1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-*N*-(2-methylbenzyl)-1-phenylpropan-1-amine (23)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 2-Methylbenzylamine **23a** (194 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (5 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**23**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 325 mg (80%) of (+)-**23** as a very viscous, yellow oil. The product was further purified by Kugelrohr distillation (135 °C, 3.4 x 10^{-5} mm Hg) to afford 325 mg (75%) of (+)-**23** as a very viscous, light yellow oil.

Data for (+)-**23**:

b.p.: 135 °C (3.4 x 10^{-5} mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.45 (dd, *J* = 6.8, 1.9 Hz, 1H, HC(7)), 7.38 – 7.33 (m, 5H, HC(8), HC(10), HC(20) and HC(22)), 7.31 – 7.27 (m, 1H, HC(16)), 7.26 – 7.19 (m, 5H, HC(9), HC(15) and HC(21)), 3.95 – 3.84 (m, 3H, HC(1) and HC(17)), 3.67 (d, *J* = 13.1 Hz, 1H, HC(5'')), 3.61 (d, *J* = 13.1 Hz, 1H, HC(5')), 3.09 (qd, *J* = 7.0, 3.6 Hz, 1H, HC(2)), 2.38 (s, 3H, H_3C(12)), 2.00 (s, 1H, HN(4)), 1.26 (d, *J* = 6.9 Hz, 6H, H_3C(18')), 1.22 (d, *J* = 6.8 Hz, 6H, H_3C(18))), 1.15 (d, *J* = 7.0 Hz, 3H, H_3C(3))).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.7 (C(14)), 141.8 (C(19)), 138.8 (C(6)), 136.7 (C(11)), 131.0 (C(13)), 130.3 (HC(21)), 129.3 (HC(10)), 128.6 (HC(7)), 128.4 (HC(19)), 127.9 (HC(9)), 127.3 (HC(16)), 127.1 (HC(8)), 126.1 (HC(20)), 123.7 (HC(15)), 65.9 (HC(1)), 53.5 (HC(2)), 50.2 (H_2C(5)), 31.7 (HC(17)), 24.6 (H_3C(18) and H_3C(18')), 19.3 (H_3C(12)), 14.7 (H_3C(3)).

IR: (neat)

3058 (w), 3022 (w), 2961 (m), 2925 (w), 2866 (w), 1603 (w), 1574 (w), 1492 (w), 1453 (m), 1382 (w), 1361 (m), 1305 (w), 1246 (w), 1178 (w), 1131 (w), 1079 (w), 1052 (m), 1029 (w), 969 (w), 928 (w), 801 (m), 743 (s), 704 (s), 643 (w), 586 (w), 551 (w), 509 (w).

LRMS: (EI, 70 eV)

77.0 (19), 79.1 (11), 91.1 (38), 103.1 (14), 104.1 (27), 105.1 (95), 106.1 (14), 115.1 (27), 116.1 (10), 117.1 (35), 118.1 (17), 123.0 (12), 128.1 (10), 134.0 (15), 135.0 (19), 137.0 (18), 149.0 (95), 150.0 (12), 151.1 (27), 175.1 (14), 177.1 (20), 179.1 (28), 191.1 (23), 192.1 (21), 193.1 (16), 194.1 (25), 210.1 (100), 211.1 (16), 219.1 (27).

HRMS: (EI, 70 eV)

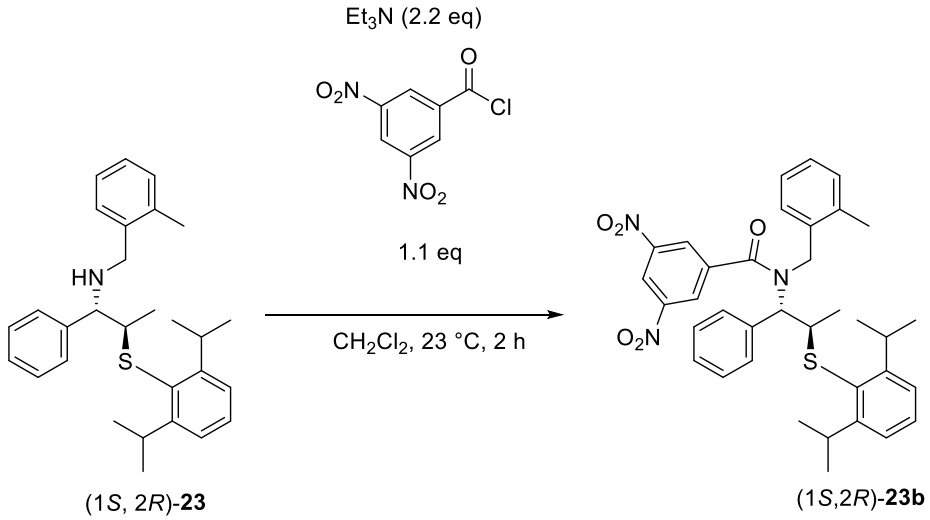
Calcd for $C_{29}H_{37}NS$ ($[M]^+$): 431.2647, Found: 231.2629

TLC: R_f 0.46 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ +32.6 (*c* = 1.84, $CHCl_3$)

SFC: t_R 11.6 min (97.6%); t_R 13.8 min (2.4%) ((Regis (*R*,*R*)-Whelk O1, CO_2/MeOH, gradient 5% MeOH/CO_2 to 20% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C) [Determined with (1*S*,2*R*)-**23b**]

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-*N*-(2-methylbenzyl)-3,5-dinitrobenzamide (23b)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**23** (15.0 mg, 0.034 mmol, 1.0 equiv), CH_2Cl_2 (300 μL), Et_3N (11 μL, 0.076 mmol, 2.2 equiv) and 3,5-dinitrobenzoyl chloride (9 mg, 0.04 mmol, 1.1 equiv) and the mixture was stirred at 23 °C for 2 h. A homogeneous, yellow solution resulted which slowly formed a precipitate over the course of the reaction. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **23b**. The product was purified by chromatography (6 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 16 mg (74%) of **23b** as a white solid.

Data for **23b**:

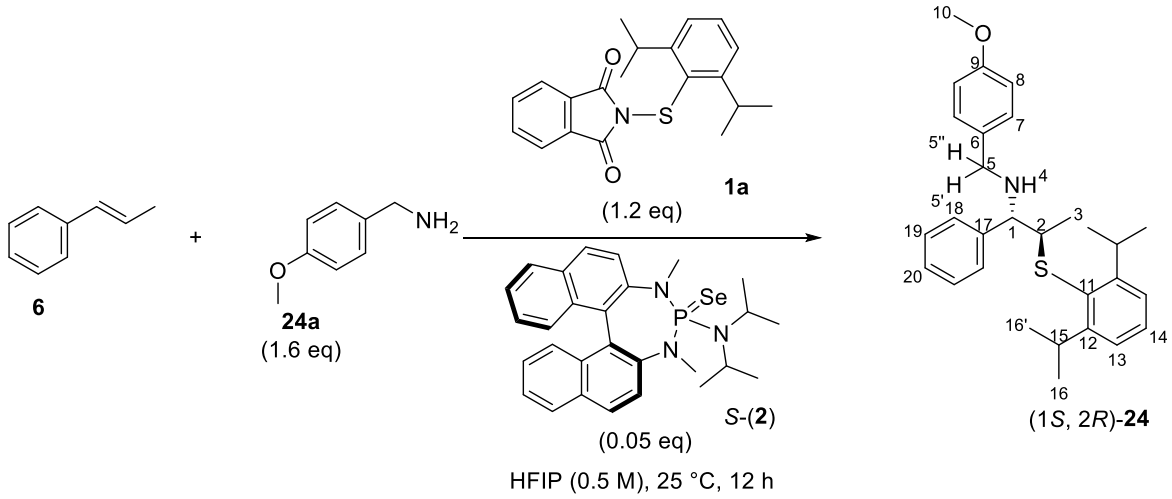
^{1}H NMR: (500 MHz, DMSO-d_6)

8.69 (s, 1H), 8.27 (d, J = 2.5 Hz, 2H), 7.58 (d, J = 6.5 Hz, 2H), 7.34 (t, J = 7.2 Hz, 5H), 7.23 – 7.16 (m, 2H), 6.95 – 6.76 (m, 3H), 6.51 (d, J = 7.6 Hz, 1H), 5.44 (br s, 1H), 4.71 – 4.46 (m, 2H), 4.14 (dd, J = 11.6, 6.2 Hz, 1H), 3.81 – 3.67 (m, 2H), 1.80 (s, 3H), 1.31 (d, J = 6.3 Hz, 3H), 1.13 (dd, J = 10.9, 6.4 Hz, 12H).

HRMS: (EI, 70 eV)

Calcd for $C_{36}H_{39}N_3O_5S$ ($[M]^+$): 625.2610, Found: 625.2611

Preparation of (1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-*N*-(4-methoxybenzyl)-1-phenylpropan-1-amine (24)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), (4-methoxyphenyl)benzylamine **24a** (219 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford

crude (+)-**24**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 305 mg (68%) of (+)-**24** as a white foam. Recrystallization from 50 °C ethanol provided 286 mg (64%) of analytically pure (+)-**24** as white, fluffy crystals.

Data for (+)-**24**:

m.p.: 98–99 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.38 – 7.31 (m, 7H, HC(19), HC(18), HC(17), HC(14) and HC(13)), 7.30 – 7.25 (m, 1H, HC(20)), 7.21 (d, J = 6.8 Hz, 2H, HC(8)), 6.93 (d, J = 8.0 Hz, 2H, HC(7)), 3.93 – 3.84 (m, 5H, H_3C(10) and HC(15)), 3.83 (d, J = 3.7 Hz, 1H, HC(1)), 3.65 (d, J = 12.9 Hz, 1H, H_2C(5’’)), 3.51 (d, J = 12.8 Hz, 1H, H_2C(5’)), 3.08 (qd, J = 7.3, 4.0 Hz, 1H, HC(2)), 2.05 (s, 1H, HN(4)), 1.26 (d, J = 6.8 Hz, 6H, H_3C(16’)), 1.22 (d, J = 6.9 Hz, 6H, H_3C(16)), 1.14 (d, J = 5.9 Hz, 3H, H_3C(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

158.8 (C(9)), 153.7 (C(12)), 141.7 (C(17)), 133.0 (C(6)), 131.0 (C(11)), 129.3 (HC(19)), 129.3 (HC(14)), 128.3 (HC(13)), 127.9 (HC(18)), 127.2 (HC(20)), 123.7 (HC(8)), 113.9 (HC(7)), 65.3 (HC(1)), 55.5 (H_3C(10)), 53.3 (HC(2)), 51.5 (H_2C(5)), 31.7 (HC(15)), 24.6 (H_3C(16) and H_3C(16’), 14.7 (H_3C(3)).

IR: (neat)

2961 (w), 2930 (w), 1612 (w), 1584 (w), 1509 (m), 1489 (w), 1462 (m), 1451 (m), 1371 (w), 1358 (w), 1302 (w), 1270 (w), 1243 (m), 1217 (m), 1179 (m), 1172 (m), 1136 (w), 1099 (w), 1079 (w), 1051 (w), 1036 (m), 972 (w), 930 (w), 834 (w), 814 (s), 805 (m), 753 (s), 704 (s), 654 (w), 632 (w), 590 (w), 557 (w), 528 (w), 511 (m), 480 (w).

LRMS: (EI, 70 eV)

119.1 (22.7), 191.1 (18.1), 269.1 (17.6), 311.2 (100.0), 312.2 (40.7), 313.2 (13.0), 448.3 (13.2).

TLC: R_f 0.24 (silica gel, hexanes/EtOAc, 12:1, UV/CAM)

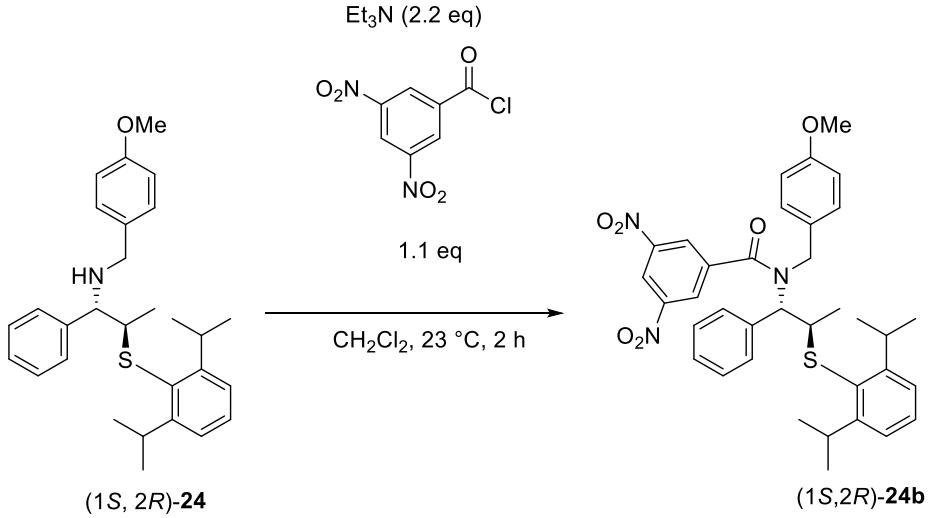
Opt. Rot.: $[\alpha]_D^{24}$ +85.5 (*c* = 1.03, $CHCl_3$)

SFC: t_R 29.7 min (97.9%); t_R 47.1 min (2.1%) (Regis (*R*,*R*)-Whelk O1, CO_2/MeOH, 90:10, 2.5 mL/min, 220 nm, 24 °C) [Determined with derivative **24b**]

Analysis: $C_{29}H_{37}NOS$ (447.68)

Calcd:	C, 77.81%;	H, 8.33%;	N, 3.13%
Found:	C, 77.40%;	H, 8.41%;	N, 3.36%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-*N*-(4-methoxybenzyl)-3,5-dinitrobenzamide (24b)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**24** (15.0 mg, 0.033 mmol, 1.0 equiv), CH_2Cl_2 (300 μL), Et_3N (10 μL, 0.08 mmol, 2.2 equiv) and 3,5-dinitrobenzoyl chloride (8.50 mg, 0.04 mmol, 1.1 equiv) and the mixture was stirred at 23 °C for 2 h. A homogeneous, yellow solution resulted which slowly formed a precipitate over the course of the reaction. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **24b**. The product was purified by

chromatography (6 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 17 mg (79%) of **24b** as a white solid.

Data for **24b**:

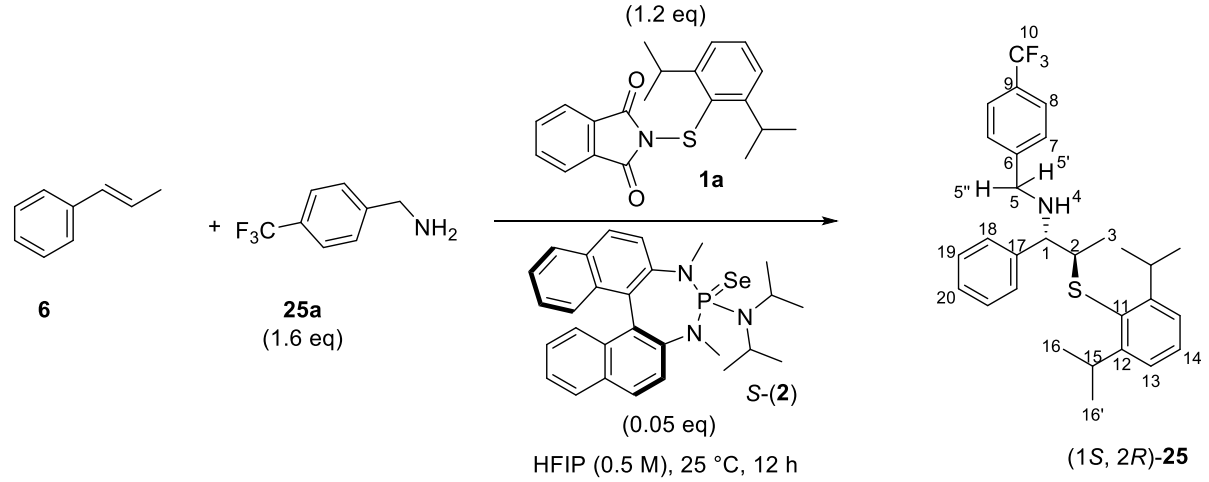
^{1}H NMR: (500 MHz, DMSO-d_6)

8.69 (s, 1H), 8.06 (d, J = 2.3 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.53 – 7.38 (m, 4H), 7.35 (t, J = 7.7 Hz, 1H), 7.20 (d, J = 7.7 Hz, 2H), 6.51 (d, J = 8.1 Hz, 2H), 6.26 (d, J = 8.3 Hz, 2H), 5.57 (s, 1H), 4.54 (d, J = 16.5 Hz, 1H), 4.31 (d, J = 16.5 Hz, 1H), 4.07 (dd, J = 11.4, 5.8 Hz, 1H), 3.76 (p, J = 6.8 Hz, 2H), 3.58 (s, 3H), 1.30 – 1.20 (m, 3H), 1.14 (d, J = 6.2 Hz, 12H).

HRMS: (EI, 70 eV)

Calcd for $C_{36}H_{39}N_3O_6S$ ([M]$^+$): 641.2560, Found: 641.2574

Preparation of (1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenyl-*N*-(4-(trifluoromethyl)benzyl)propan-1-amine (25)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), (4-(trifluoromethyl)phenyl)methanamine **25a** (280 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (S)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The

layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (4 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**25**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 325 mg (67%) of (+)-**25** as an off white foam. The product was purified by trituration as follows. The crude material was suspended in ethanol (1 mL) and sonicated at 23 °C and cooled to -20 °C for 4 h. Vacuum filtration of this suspension yielded 296 mg (61%) of analytically pure (+)-**25** as a fine, white powder.

Data for (+)-**25**:

m.p.: 51–53 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.63 (d, *J* = 8.0 Hz, 2H, HC(8)), 7.53 (d, *J* = 7.9 Hz, 2H, HC(7)), 7.39 – 7.33 (m, 3H, HC(14) and HC(18)), 7.33 – 7.26 (m, 3H, HC(19) and HC(20)), 7.21 (d, *J* = 7.7 Hz, 2H, HC(13)), 3.88 (sept, *J* = 6.8 Hz, 2H, HC(15)), 3.84 (d, *J* = 3.7 Hz, 1H, HC(1)), 3.77 (d, *J* = 13.8 Hz, 1H, HC(5'')), 3.64 (d, *J* = 13.7 Hz, 1H, HC(5')), 3.11 (qd, *J* = 7.0, 3.6 Hz, 1H, HC(2)), 2.16 (br s, 1H, HN(4)), 1.25 (d, *J* = 6.9 Hz, 6H, H_3C(16')), 1.22 (d, *J* = 6.9 Hz, 6H, H_3C(16)), 1.16 (d, *J* = 7.0 Hz, 3H, H_3C(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.51 (C(12)), 144.8 (C(6)), 141.1 (C(17)), 130.6 (C(11)), 129.3 (CH(14)), 129.2 (q, *J*=32.2 Hz, 1C, C(9)), 128.3 (HC(18)), 128.8 (HC(20)), 127.7 (HC(7)), 127.9 (HC(19)), 125.3 (q, *J*= 3.8 H, 1C, HC(8)), 124.3 (q, *J*=271.9, 1C, C(10)), 123.6 (HC(13)), 65.1 (HC(1)), 53.0 (HC(2)), 51.4 (H_2C(5)), 31.6 (HC(15)), 24.5 (H_3C(16')), 24.4 (H_3C(16)), 14.5 (H_3C(3)).

^{19}F NMR: (470 MHz, $CDCl_3$)

-62.35.

IR: (neat)

2966 (w), 2929 (w), 2865 (w), 1617 (w), 1578 (w), 1490 (w), 1454 (m), 1416 (w), 1372 (w), 1360 (w), 1324 (s), 1250 (w), 1224 (w), 1177 (w), 1159 (s), 1129 (s), 1108 (m), 1098 (m), 1081 (m), 1066 (s), 1052 (m), 1030 (m), 1018 (m), 972 (w), 953 (w), 920 (w), 840 (m), 822 (m), 804 (m), 778 (m), 746 (m), 722 (w), 703 (s), 656 (w), 638 (w), 595 (w), 587 (w), 532 (w), 512 (w), 495 (w), 459 (w).

LRMS: (EI, 70 eV)

119.1 (24.6), 191.1 (19.4), 269.1 (14.4), 311.2 (100.0), 312.2 (27.1).

TLC: R_f 0.55 (silica gel, hexanes/EtOAc, 23:2, UV/CAM)

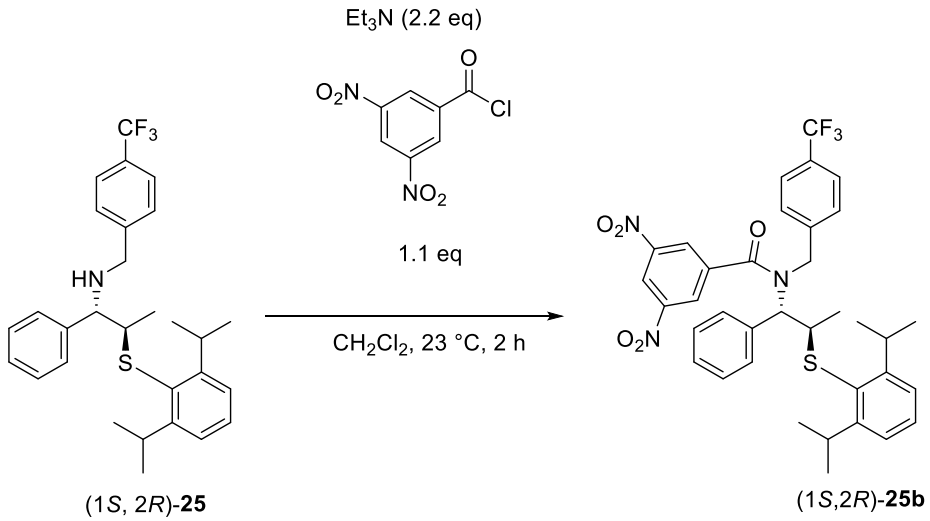
Opt. Rot.: $[\alpha]_D^{24}$ +33.8 (c = 1.04, $CHCl_3$)

SFC: t_R 10.8 min (97.1%); t_R 12.8 min (2.8%) ((Regis (*R,R*)-Whelk O1, CO_2/MeOH, gradient 5% MeOH/CO_2 to 20% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C) [Determined with derivative **25b**]

Analysis: $C_{29}H_{34}F_3NS$ (485.65)

Calcd:	C, 71.72%;	H, 7.06%;	N, 2.88%
Found:	C, 71.41%;	H, 7.16%;	N, 2.99%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-3,5-dinitro-*N*-(4-(trifluoromethyl)benzyl)benzamide (25b)



(1*S*, 2*R*)-**25** (1*S*,2*R*)-**25b**

A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**25** (15.0 mg, 0.030 mmol, 1.0 equiv), CH_2Cl_2 (300 μL), Et_3N (9 μL, 0.068 mmol, 2.2 equiv) and

3,5-dinitrobenzoyl chloride (7.8 mg, 0.034 mmol, 1.1 equiv) and the mixture was stirred at 23 °C for 2 h. A homogeneous, yellow solution resulted which slowly formed a precipitate over the course of the reaction. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **25b**. The crude material was dissolved in EtOAc (2 mL) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure (15 mmHg, 30 C) to afford 16 mg (76%) of **25b** as an yellow solid.

Data for **25b**:

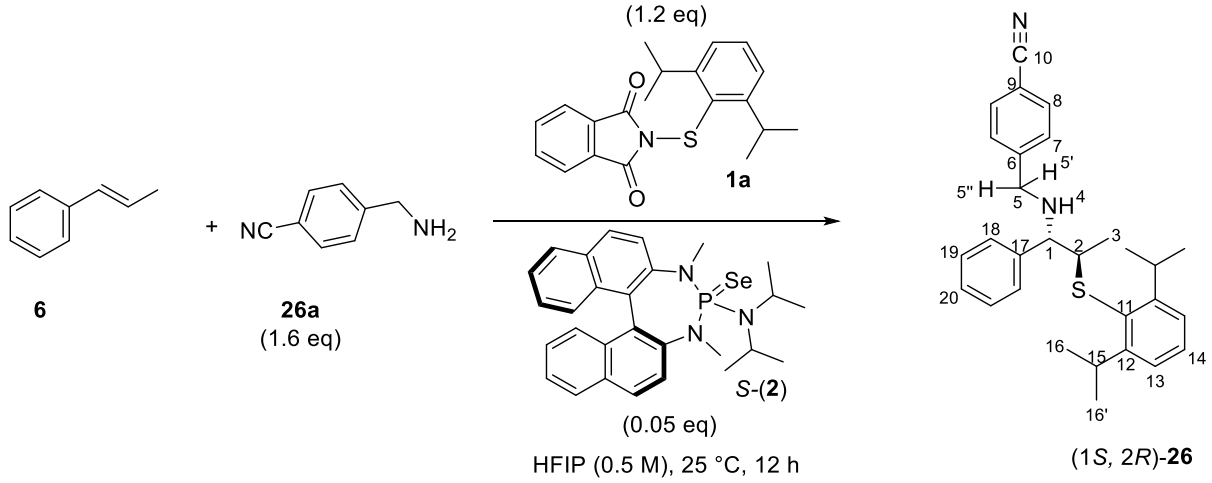
^{1}H NMR: (500 MHz, DMSO-d6, 80 °C)

8.76 (br s, 1H), 8.28 (br s, 2H), 7.56 (br s, 2H), 7.33 (m, 6H), 7.15 (d, J = 7.6 Hz, 2H), 6.81 (br s, 2H), 4.74 (m, 2H), 4.05 (br s, 1H), 3.69 (br s, 2H), 1.22 (br s, 3H), 1.15 – 0.95 (m, 12H).

HRMS: (EI, 70 eV)

Calcd for $C_{36}H_{36}N_3O_5SF_3$ ($[M]^+$): 679.2328, Found: 679.2319

Preparation of 4-((((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)amino)methyl)benzonitrile (26)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-

(aminomethyl)benzonitrile **26a** (211 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (S)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**26**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford (+)-**26** as a yellow oil. Sonication in ethanol (1 mL) precipitated (+)-**26** as a fine, white powder to afford 334 mg (76%) of (+)-**26**. The suspension was concentrated under reduced pressure (15 mm Hg, 30 °C) Recrystallization from 50 °C ethanol (1.5 ml) afforded 310 mg (70%) of analytically pure (+)-**26** as white crystals.

Data for (+)-**26**:

m.p.: 60–62 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.66 (d, *J* = 8.2 Hz, 2H, HC(8)), 7.53 (d, *J* = 8.1 Hz, 2H, (HC(7)), 7.35 (m, 3H HC(14) and HC(18)), 7.28 (m, 3H, HC(20) and HC(19)), 7.21 (d, *J* = 7.7 Hz, 2H, HC(13)), 3.86 (hept, *J* = 6.9 Hz, 2H, (HC(15)), 3.82 (d, *J* = 3.6 Hz, 1H, HC(1)), 3.76 (d, *J* = 14.4 Hz, 1H, HC(5'')), 3.64 (d, *J* = 14.3 Hz, 1H, HC(5')), 3.11 (qd, *J* = 7.0, 3.6 Hz, 1H, HC(2)), 2.17 (br s, 1H, HN(4)), 1.24 (d, *J* = 6.8 Hz, 6H, H_3C(16')), 1.22 (d, *J* = 6.9 Hz, 6H, H_3C(16)), 1.15 (d, *J* = 7.0 Hz, 3H, H_3C(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.5 (C(12)), 146.3 (C(6)), 140.9 (C(17)), 132.2 (HC(8)), 130.4 (C(11)), 129.3 (HC(14)), 128.5 (HC(7)), 128.4 (HC(18)), 127.6 (HC(20)), 127.4 (HC(19)), 123.7 (HC(13)), 119.0 (C(10)), 110.7 (C(9)), 65.1 (HC(1)), 52.9 (HC(2)), 51.4 (H_2C(5)), 31.6 (HC(15)), 24.5 (H_3C(16')), 24.4 (H_3C(16)), 14.5 (H_3C(3)).

IR: (neat)

2968 (w), 2932 (w), 2225 (w), 1606 (w), 1491 (w), 1452 (m), 1370 (w), 1359 (w), 1306 (w), 1282 (w), 1214 (w), 1193 (w), 1179 (w), 1132 (w), 1096 (w), 1078 (w), 1066 (w), 1051 (w), 1030 (m), 1022 (w), 970 (w), 953 (w), 928 (w), 841 (m), 818 (m), 803 (m), 774 (s), 761 (m), 746 (m), 711 (s), 655 (w), 639 (w), 588 (w), 548 (m), 536 (w), 512 (w), 487 (w).

LRMS: (EI, 70 eV)

119.1 (35.8), 191.1 (27.9), 269.1 (19.5), 311.2 (100.0), 312.2 (27.6).

TLC: R_f 0.28 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

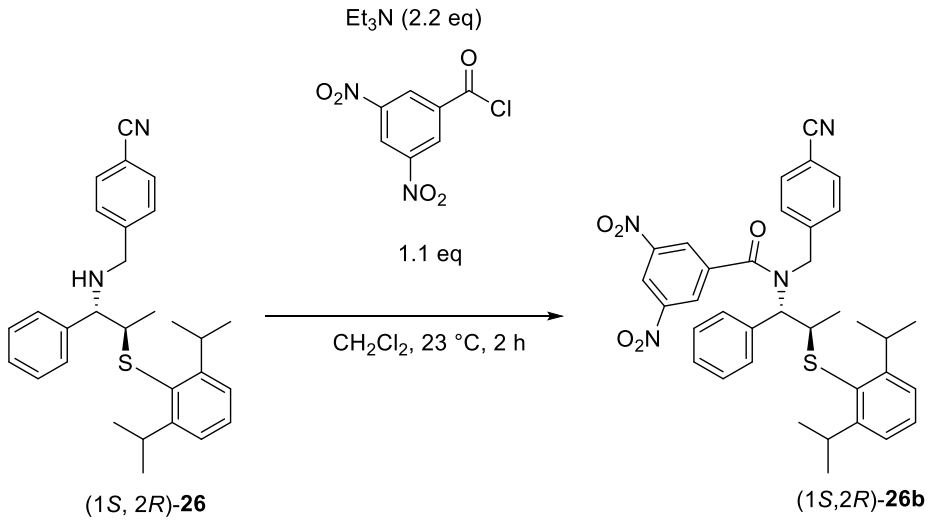
Opt. Rot.: $[\alpha]_D^{24}$ +28.9 (c = 1.23, $CHCl_3$)

SFC: t_R 11.9 min (96.4%); t_R 18.8 min (3.6%) ((Regis (*R*,*R*)-Whelk O1, CO_2/MeOH, 85:15, 2.5 mL/min, 220 nm, 24 °C) [Determined with derivative **26b**]

Analysis: $C_{29}H_{34}N_2S$ (442.66)

Calcd:	C, 78.69%;	H, 7.74%;	N, 6.33%
Found:	C, 78.35%;	H, 7.67%;	N, 6.41%

Preparation of *N*-(4-Cyanobenzyl)-*N*-((1*S*,2*R*)-2-((2,6-diisopropylphenyl)thio)-1-phenylpropyl)-3,5-dinitrobenzamide (26b)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**26** (15.0 mg, 0.034 mmol, 1.0 equiv), CH_2Cl_2 (300 μL), Et_3N (11 μL, 0.076 mmol, 2.2 equiv)

and 3,5-dinitrobenzoyl chloride (8.5 mg, 0.04 mmol, 1.1 equiv) and the mixture was stirred at 23 °C for 2 h. A homogeneous, yellow solution resulted which slowly formed a precipitate over the course of the reaction. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **26b**. The crude material was dissolved in EtOAc (2 mL) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure (15 mmHg, 30 C) to afford 19 mg (88%) of **26b** as an off white solid.

Data for **26b**:

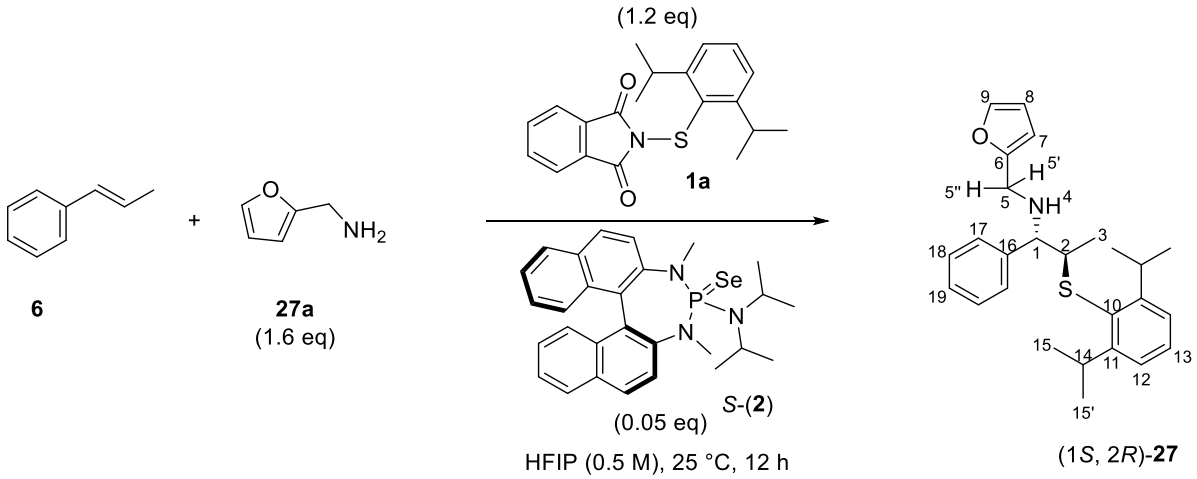
^{1}H NMR: (500 MHz, DMSO-d_6)

8.74 – 8.63 (m, 1H), 8.20 (d, J = 2.1 Hz, 2H), 7.69 – 7.57 (m, 3H), 7.48 – 7.25 (m, 9H), 7.14 (dd, J = 15.7, 7.8 Hz, 2H), 6.62 (d, J = 7.9 Hz, 2H), 5.69 (s, 1H), 4.78 (d, J = 18.1 Hz, 2H), 4.58 (d, J = 17.8 Hz, 1H), 4.07 (dt, J = 12.9, 6.5 Hz, 1H), 3.76 (br s, 2H), 3.46 (br s, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 6.7 Hz, 12H).

HRMS: (EI, 70 eV)

Calcd for $C_{36}H_{36}N_4O_5S$ ([M]$^+$): 636.2394, Found: 636.2406

Preparation of (1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-*N*-(furan-2-ylmethyl)-1-phenylpropan-1-amine (27)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)-2*-methyl styrene **6** (118.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), furan-2-ylmethanamine **27a** (155 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (S)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**27**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 325 mg (80%) of (+)-**27** as a yellow oil that solidified on standing. Recrystallization from 50 °C ethanol (1.5 ml) afforded 306 mg (75%) of analytically pure (+)-**27** as white crystals.

Data for (+)-**27**:

m.p.: 50–52 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.42 – 7.37 (m, 1H, HC(9)), 7.32 (m, 5H, HC(17), HC(18) and HC(19)), 7.28 – 7.23 (m, 1H, HC(13)), 7.18 (d, *J* = 7.7 Hz, 2H, HC(12)), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H, HC(8)), 6.17 (d, *J* = 3.1 Hz, 1H, HC(7)), 3.86 (hept, *J* = 6.7 Hz, 2H, HC(14)), 3.79 (d, *J* = 4.1 Hz, 1H, HC(1)), 3.69 (d, *J* = 14.2 Hz, 1H, HC(5'')), 3.55 (d, *J* = 14.1 Hz, 1H, HC(5'')), 3.08 (dq, *J* = 6.9, 4.0 Hz, 1H, HC(2)), 2.21 (br s, 1H, HN(4)), 1.23 (d, *J* = 6.9 Hz, 6H, H_3C(15')), 1.20 (d, *J* = 6.8 Hz, 6H, H_3C(15)), 1.11 (d, *J* = 7.1 Hz, 3H, H_3C(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

154.0 (C(6)), 153.6 (C14)), 141.7 (HC(9)), 141.1 (C(16)), 130.6 (C(10)), 129.1 (HC(19)), 128.2 (HC(18)), 127.8 (HC(17)), 127.2 (HC(13)), 123.6 (HC(12)), 110.1 (HC(8)), 106.6 (HC(7)), 65.1 (HC(1)), 52.8 (HC(2)), 44.6 (H_2C(5)), 31.6 (H_3C(14)), 24.4 (H_3C(15) and H_3C(15')), 14.6 (H_3C(3)).

IR: (neat)

2958 (m), 2863 (w), 1574 (w), 1489 (w), 1452 (m), 1380 (w), 1359 (w), 1348 (w), 1259 (w), 1181 (w), 1151 (m), 1078 (m), 1052 (w), 1031 (w), 1014 (m), 952 (w), 913 (w), 885 (m), 804 (m), 760 (s), 748 (s), 736 (s), 708 (s), 613 (w), 601 (m), 581 (w), 525 (w), 506 (m), 462 (w),

LRMS: (EI, 70 eV)

119.1 (39.6), 191.1 (29.3), 269.1 (19.1), 311.2 (100.0), 312.2 (26.3).

TLC: R_f 0.41 (silica gel, hexanes/EtOAc, 12:1, UV/CAM)

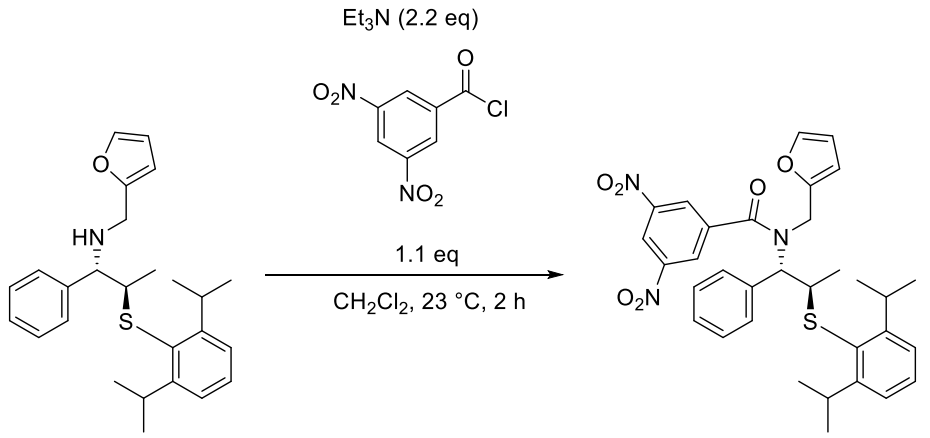
Opt. Rot.: $[\alpha]_D^{24}$ +96.3 (c = 1.07, $CHCl_3$)

SFC: t_R 14.5 min (1.6%); t_R 15.8 min (98.4%) (Chiralpak OD, MeOH/CO_2, Gradient 5% MeOH/CO_2 to 20% MeOH/CO_2 over 10 min; 20% MeOH/CO_2 2.5 mL/min, 220 nm, 24 °C) [Determined with derivative **27b**]

Analysis: $C_{26}H_{33}NOS$ (407.61)

Calcd:	C, 76.61%;	H, 8.16%;	N, 3.44%
Found:	C, 73.77%;	H, 8.27%;	N, 3.67%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-*N*-(furan-2-ylmethyl)-3,5-dinitrobenzamide (27b)



(1*S*, 2*R*)-**27** (1*S*,2*R*)-**27b**

A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**27** (15.0 mg, 0.037 mmol, 1.0 equiv), CH_2Cl_2 (300 μL), Et_3N (11 μL, 0.09 mmol, 2.2 equiv) and 3,5-dinitrobenzoyl chloride (9.50 mg, 0.04 mmol, 1.1 equiv) and the mixture was stirred at 23 °C for 2 h. A homogeneous, yellow solution resulted which slowly formed a precipitate over the

course of the reaction. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **27b**. The product was purified by chromatography (6 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 17 mg (76%) of **27b** as a white solid.

Data for **27b**:

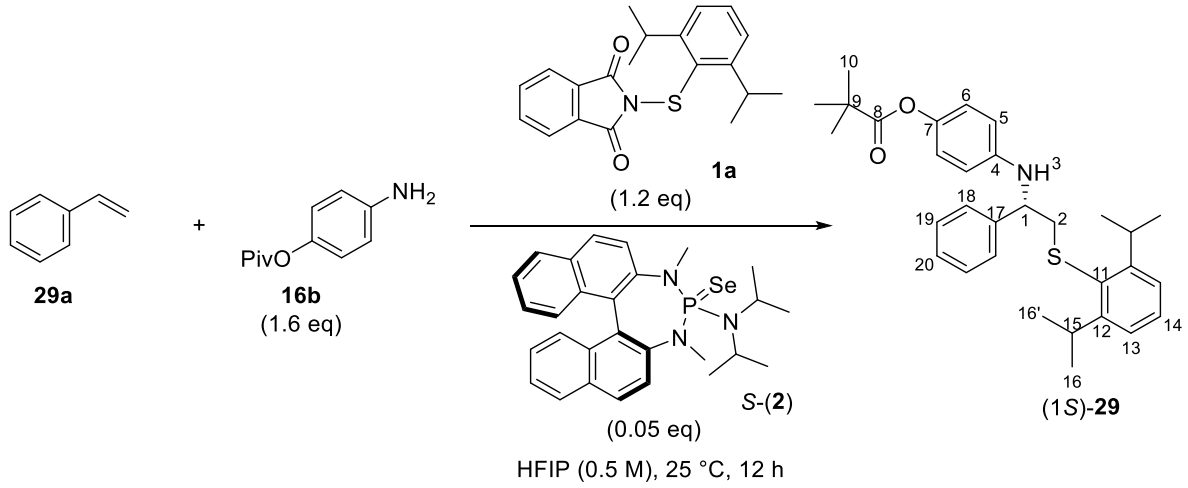
^{1}H NMR: (500 MHz, DMSO-d_6)

8.83 (s, 1H), 8.47 (d, J = 2.1 Hz, 2H), 7.57 (d, J = 7.4 Hz, 2H), 7.44 (d, J = 1.8 Hz, 2H), 7.42 – 7.34 (m, 3H), 7.30 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 7.7 Hz, 2H), 6.29 (dd, J = 3.2, 1.8 Hz, 1H), 6.06 (d, J = 3.3 Hz, 1H), 5.23 (s, 1H), 4.42 (d, J = 17.3 Hz, 1H), 4.33 (d, J = 16.7 Hz, 1H), 4.05 (dq, J = 12.5, 6.6 Hz, 1H), 3.70 (p, J = 7.0 Hz, 2H), 1.10 (d, J = 6.7 Hz, 12H), 1.07 (d, J = 6.6 Hz, 3H).

HRMS: (EI, 70 eV)

Calcd for $C_{33}H_{35}N_3O_6S$ ([M]$^+$): 601.2247, Found: 601.2234

Preparation of (*S*)-4-((2-((2,6-Diisopropylphenyl)thio)-1-phenylethyl)amino)phenyl pivalate (29)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with styrene **29a** (104.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16b** (309 mg, 1.60 mmol, 1.60 eq.) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**29**. The product was purified by chromatography (66 g silica gel, 3.5 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 97:3) to afford 421 mg (86%) of impure (+)-**29** as an off white foam. The product was purified by trituration as follows. The crude material was suspended in methanol (2.5 mL) and sonicated at 23 °C and cooled to -20 °C for 12 h. Vacuum filtration of this suspension yielded 389 mg (80%) of analytically pure (+)-**29** as a fine, white powder.

Data for (+)-**29**:

m.p.: 108–109 °C (methanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.36 – 7.27 (m, 5H, HC(18), HC(19) and HC(14)), 7.25 – 7.21 (m, 1H, HC(20)), 7.16 (d, *J* = 7.7 Hz, 2H, HC(13)), 6.74 (d, *J* = 8.8 Hz, 2H, HC(6)), 6.41 (d, *J* = 8.8 Hz, 2H, HC(5)), 4.46 (d, *J* = 3.4 Hz, 1H, HC(3)), 4.23 (dt, *J* = 9.5, 3.7 Hz, 1H, HC(1)), 3.83 (hept, *J* = 6.9 Hz, 2H, HC(15)), 3.02 (dd, *J* = 13.4, 4.0 Hz, 1H, $H_2C(2'')$), 2.92 (dd, *J* = 13.4, 9.5 Hz, 1H, $H_2C(2')$), 1.30 (s, 9H, $H_3C(10)$), 1.19 (d, *J* = 6.8 Hz, 6H, $H_3C(16')$), 1.11 (d, *J* = 6.8 Hz, 6H, $H_3C(16)$).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.6 (C(8)), 153.3 (C(12)), 144.9 (C(17)), 142.7 C(7)), 142.5 (C(4)), 130.4 (C(11)), 129.4 (HC(14)), 128.8 (HC(19)), 127.5 (HC(20)), 126.2 (HC(18)), 123.8 (HC(13)), 121.7 (HC(6)), 114.0 (HC(5)), 58.2 (HC(1)), 45.9 ($H_2C(2)$), 38.9 (C(9)), 31.6 (HC(15)), 27.2 ($H_3C(10)$), 24.6 ($H_3C(16')$), 24.2 (($H_3C(16)$).

IR: (neat)

2963 (w), 2867 (w), 1749 (m), 1615 (w), 1511 (s), 1478 (w), 1462 (w), 1395 (w), 1355 (w), 1314 (w), 1278 (w), 1200 (m), 1164 (w), 1112 (s), 1050 (w), 1027 (w), 927 (w), 885 (w), 838 (w), 804 (m), 765 (w), 743 (m), 721 (m), 698 (w), 631 (w), 573 (w), 516 (m).

LRMS: (EI, 70 eV)

57.1 (46), 77.0 (30), 80.1 (12), 91.1 (33), 103.1 (13), 104.1 (23), 105.0 (52), 105.1 (15), 108.0 (14), 109.1 (83), 115.1 (13), 128.1 (12), 134.0 (15), 135.0 (22), 147.0 (10), 149.0 (89), 150.1 (11), 163.1 (53), 175.1 (13), 177.1 (12), 179.1 (14), 191.1 (26), 192.1 (15), 193.1 (24), 194.1 (11), 197.1 (24), 198.1 (32), 282.2 (100), 283.2 (20), 296.2 (38), 297.2 (12).

TLC: R_f 0.21 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

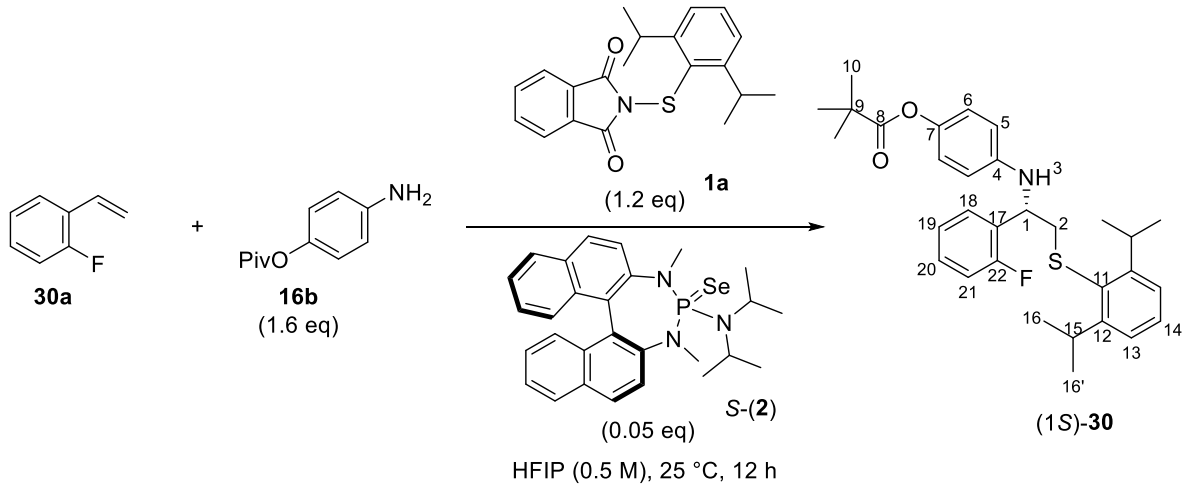
Opt. Rot.: $[\alpha]_D^{24}$ +60.1 (c = 1.21, $CHCl_3$)

SFC: t_R 14.8 min (95.4%); t_R 17.8 min (4.6%) %) (Chiralpak OJ, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{31}H_{39}NO_2S$ (489.71)

Calcd:	C, 76.03%;	H, 8.03%;	N, 2.86%
Found:	C, 75.85%;	H, 8.23%;	N, 2.82%

Preparation of 4-(((1*S*)-2-((2,6-Diisopropylphenyl)thio)-1-(2-fluorophenyl)propyl)amino)phenyl Pivalate (30)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with 1-fluoro-2-vinylbenzene **30a** (120.0 mg, 1.0 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16b** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 95:5, UV/$KMnO_4$). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**30**. The product was purified by chromatography (66 g silica gel, 3.5 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford 431 mg (85%) of (+)-**30** as a bright yellow solid. The product was purified by trituration as follows. The crude material was suspended in methanol (2 mL) and sonicated at 23 °C and cooled to -20 °C for 4 h. Vacuum filtration of this suspension yielded 322 mg (61%) of analytically pure (+)-**30** as a fine, bright yellow powder. The mother liquor was collected and concentrated under reduced pressure (15 mm Hg, 30 °C) to give a yellow-orange solid which was suspended in methanol (1 mL) and sonicated at 23 °C and cooled to -20 °C for 1 hour to afford an additional 81 mg (16%) of analytically pure (+)-**30** as a fine, bright yellow powder.

Data for (+)-**30**:

m.p.: 98–99 °C (methanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.39 (td, *J* = 7.7, 1.8 Hz, 1H, HC(18)), 7.31 (t, *J* = 7.7 Hz, 1H, HC(14)), 7.21 (tdd, *J* = 7.4, 5.2, 1.8 Hz, 1H, HC(20)), 7.15 (d, *J* = 7.7 Hz, 2H, HC(13)), 7.06 (td, *J* = 7.5, 1.2 Hz, 1H, HC(19)), 7.01 (ddd, *J* = 10.8, 8.1, 1.2 Hz, 1H, HC(21)), 6.77 (d, *J* = 8.8 Hz, 2H, HC(6)), 6.43 (d, *J* = 8.9 Hz, 2H, HC(5)), 4.66 (dt, *J* = 8.9, 4.3 Hz, 1H, HC(1)), 4.39 (d, *J* = 4.6 Hz, 1H, HN(3)), 3.83 (hept, *J* = 6.9 Hz, 2H, HC(15)), 3.10 (dd, *J* = 13.2, 4.0 Hz, 1H, H_2C(2'')), 2.96 (dd, *J* = 13.2, 9.2 Hz, 1H, H_2C(2')), 1.31 (s, 9H, H_3C(10)), 1.18 (d, *J* = 6.9 Hz, 6H, H_3C(16')), 1.13 (d, *J* = 6.9 Hz, 6H, H_3C(16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.6 (C(8)), 160.3 (d, *J*=245.7 Hz, 1C, C(22)), 153.3 (C(12)), 144.4 (C(7)), 142.9 (C(4)), 130.4 (C(11)), 129.4 (HC(14)), 129.0 (d, *J* = 8.2 Hz, 1C, C(20)), 128.8 (d, *J*=12.7 Hz, 1C, C(17)), 127.9 (d, *J* = 4.3 Hz, 1C, C(18)), 124.5 (d, *J*=3.3 Hz, 1C, C(19)), 123.8 (C(13)), 121.8 (C(6)), 115.5 (d, *J* = 21.4 Hz, 1C, C(21)), 113.9 (C(5)), 52.2 (d, *J* = 2.1 Hz, 1C, C(1)), 43.8 (H_2C(2)), 38.9 (C(9)), 31.6 (HC(15)), 27.2 (H_3C(10)), 24.5 (H_3C(16')), 24.2 (H_3C(16)).

^{19}F NMR: (470 MHz, $CDCl_3$)

-119.78 (m).

IR: (neat)

3391 (w), 2963 (m), 1726 (s), 1612 (w), 1585 (w), 1511 (s), 1480 (m), 1455 (m), 1395 (w), 1384 (w), 1362 (w), 1318 (w), 1281 (m), 1194 (s), 1170 (s), 1130 (s), 1080 (m), 1052 (m), 1030 (m), 929 (w), 891 (w), 840 (m), 823 (m), 795 (s), 763 (s), 748 (s), 704 (w), 612 (w), 515 (m).

LRMS: (EI, 70 eV)

57.1 (12), 109.1 (25), 149.0 (35), 163.1 (15), 216.1 (17), 300.1 (100), 301.1 (20), 314.2 (11).

TLC: R_f 0.22 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

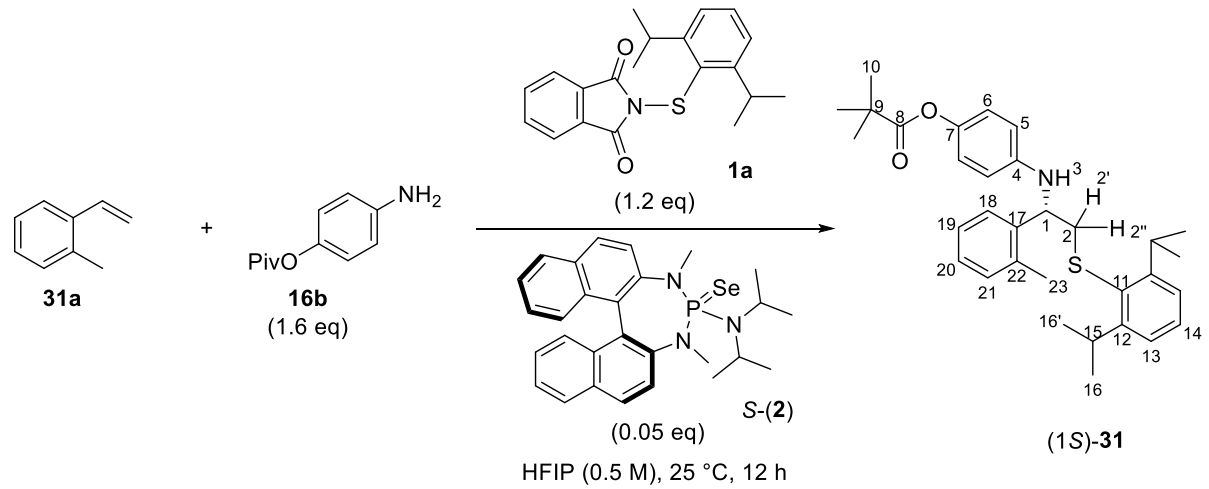
Opt. Rot.: $[\alpha]_D^{24}$ +14.1 (*c* = 1.12, $CHCl_3$)

SFC: t_R 11.5 min (89.8%); t_R 13.9 min (10.2%) (Chiralpak OJ, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{31}H_{38}FNO_2S$ (507.70)

Calcd:	C, 73.34%;	H, 7.54%;	N, 2.76%
Found:	C, 73.36%;	H, 7.67%;	N, 2.82%

Preparation of (*S*)-4-((2-((2,6-Diisopropylphenyl)thio)-1-(o-tolyl)ethyl)amino)phenyl Pivalate (31)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with 1-methyl-2-vinylbenzene **31a** (118 mg, 1.0 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16b** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 24:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**31**. The product was chromatographed (66 g silica gel, 3.5 cm column, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution: 49:1 (250 mL) to 97:3 (250 mL) to 24:1 (500 mL)) to afford 361 mg (72%) of (+)-**31** as an off white foam. The product was further purified by Kugelrohr distillation (130 °C, 3.4 x 10^{-5} mm Hg) to afford 355 mg (70%) of (+)-**31** as a white solid.

Data for (+)-**31**:

m.p.: 64–66 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.49 – 7.45 (m, 1H, HC(21)), 7.35 (t, *J* = 7.7 Hz, 1H, HC(14)), 7.18 (d, *J* = 7.7 Hz, 2H, HC(13)), 7.17 – 7.09 (m, 3H, HC(18), HC(19) and HC(20)), 6.80 – 6.74 (m, 2H, HC(6)), 6.42 – 6.34 (m, 2H, HC(5)), 4.46 (d, *J* = 2.8 Hz, 1H, HN(3)), 4.39 (dt, *J* = 9.5, 3.2 Hz, 1H, HC(1)), 3.86 (hept, *J* = 6.9 Hz, 2H, HC(15)), 2.89 (dd, *J* = 13.7, 3.7 Hz, 1H, $H_2C(2'')$), 2.84 (dd, *J* = 13.7, 9.5 Hz, 1H, $H_2C(2')$), 2.06 (s, 3H, $H_3C(23)$), 1.33 (s, 9H, $H_3C(10)$), 1.20 (d, *J* = 6.8 Hz, 6H, $H_3C(16')$), 1.12 (d, *J* = 6.8 Hz, 6H, $H_3C(16)$).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.6 (C(8)), 153.4 (C(15)), 145.2 (C(7)), 142.7 (C(4)), 139.9 (C(17)), 134.4 (C(22)), 130.8 (HC(20)), 130.5 (C(11)), 129.5 (HC(14)), 127.2 (HC(18)), 126.7 (HC(19)), 125.4 (HC(21)), 123.7 (HC(13)), 121.8 (HC(6)), 113.9 (HC(5)), 54.5 (HC(1)), 44.4 ($H_2C(2)$), 38.9 (C(9)), 31.6 (HC(15)), 27.2 ($H_3C(10)$), 24.5 ($H_3C(16')$), 24.2 ($H_3C(16)$), 18.3 ($H_3C(23)$).

IR: (neat)

3384 (w), 2962 (m), 1728 (m), 1614 (w), 1515 (s), 1480 (m), 1459 (m), 1394 (w), 1362 (w), 1320 (w), 1282 (m), 1197 (s), 1167 (m), 1127 (s), 1030 (m), 931 (w), 888 (w), 839 (w), 823 (w), 799 (m), 755 (s), 745 (m), 732 (m), 699 (w), 625 (w), 516 (m), 455 (m).

LRMS: (EI, 70 eV)

57.1 (35), 77.0 (15), 80.1 (14), 91.1 (25), 105.0 (15), 105.1 (22), 108.0 (13), 109.1 (100), 115.1 (29), 117.1 (31), 118.1 (17), 119.1 (18), 128.1 (11), 134.0 (17), 135.0 (20), 137.0 (11), 147.0 (11), 149.0 (92), 150.0 (11), 163.1 (58), 175.1 (17), 177.1 (17), 179.1 (17), 191.1 (24), 192.1 (22), 193.1 (27), 194.1 (17), 211.1 (14), 212.1 (17), 296.2 (97), 297.2 (20), 310.2 (54), 311.2 (15).

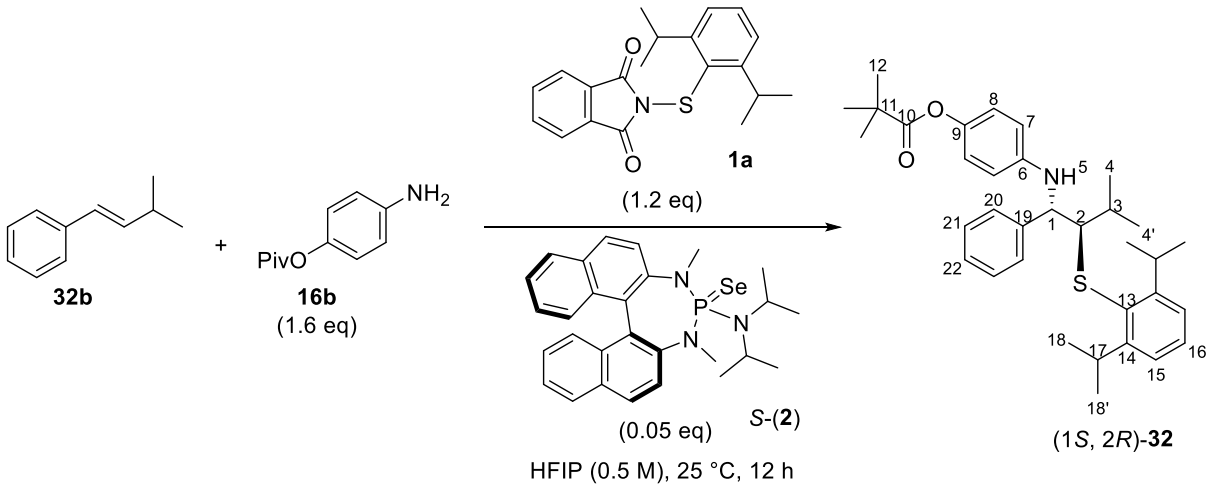
TLC: R_f 0.24 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ +6.08 (*c* = 1.04, $CHCl_3$)

SFC: t_R 10.9 min (80.1%); t_R 12.4 min (19.9%) (Chiralcel OJ, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C)

Analysis:	$C_{34}H_{45}NO_2S$ (531.79)		
Calcd:	C, 76.30%;	H, 8.20%;	N, 2.78%
Found:	C, 76.16%;	H, 8.46%;	N, 2.96%

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-3-methyl-1-phenylbutyl)amino)phenyl Pivalate (32)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)*-(3-methylbut-1-en-1-yl)benzene **32b** (146 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16b** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 12:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**32**. The product was chromatographed (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 413 mg (78%) of (+)-**32** as a viscous yellow oil. The product was further purified by Kugelrohr distillation (135 °C, 3.4 x 10^{-5} mm Hg) to afford 399 mg (75%) of (+)-**32** as a white solid.

Data for (+)-**32**:

m.p.: 60–62 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.34 (t, *J* = 7.7 Hz, 1H, HC(16)), 7.30 – 7.23 (m, 2H, HC(20)), 7.25 – 7.18 (m, 1H, HC(22)), 7.18 – 7.12 (m, 4H, HC(21) and HC(15)), 6.74 (d, *J* = 8.8 Hz, 2H, HC(8)), 6.39 (d, *J* = 8.8 Hz, 2H, HC(7)), 4.74 (d, *J* = 1.9 Hz, 1H, HN(5)), 4.04 (dd, *J* = 3.8, 1.7 Hz, 1H, HC(1)), 3.86 – 3.76 (m, 2H, HC(17)), 3.13 (dd, *J* = 3.9, 2.3 Hz, 2H, HC(2)), 2.02 (dh, *J* = 6.8, 2.3 Hz, 1H, HC(3)), 1.33 (d, *J* = 0.9 Hz, 9H, H_3C(12)), 1.28 (d, *J* = 6.8 Hz, 3H, H_3C(4')), 1.20 (d, *J* = 7.2 Hz, 6H, H_3C(18')), 1.09 (d, *J* = 6.8 Hz, 3H, H_3C(4)), 0.96 (s, 6H, H_3C(18)).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.6 (C(10)), 153.9(C(14)), 145.7 (C(6)), 142.8 (C(9)), 141.2 (C(19)), 129.8 (C(13)), 129.3 (HC(16)), 128.5 (HC(20)), 127.0 (HC(22)), 126.8 (HC(21)), 123.7 (HC(15)), 121.6 (HC(8)), 114.5 (HC(7)), 64.8 (HC(2)), 61.0 (HC(1)), 38.9 (C(11)), 31.3 (HC(17)), 27.7 (HC(3)), 27.2 (H_3C(12)), 25.1 (H_3C(18')), 23.6 (H_3C(4)), 23.5 (H_3C(18)), 19.6 (H_3C(4')).

IR: (neat)

2960 (w), 1748 (m), 1612 (w), 1508 (s), 1461 (m), 1385 (w), 1362 (w), 1310 (w), 1273 (m), 1198 (m), 1166 (m), 1117 (s), 1053 (w), 1028 (m), 927 (w), 888 (w), 837 (w), 799 (m), 766 (w), 749 (m), 702 (m), 632 (w), 592 (w), 492 (w).

LRMS: (EI, 70 eV)

57.1 (40), 65.0 (11), 77.0 (19), 80.1 (24), 91.1 (50), 103.1 (14), 105.1 (13), 108.0 (19), 109.1 (100), 115.1 (41), 116.1 (16), 117.1 (28), 123.0 (17), 127.1 (17), 128.1 (60), 129.1 (64), 130.1 (13), 131.1 (38), 134.0 (16), 135.0 (26), 137.0 (45), 143.1 (13), 144.1 (31), 145.1 (75), 146.1 (17), 149.0 (62), 151.1 (26), 163.1 (14), 175.1 (17), 177.1 (10), 179.1 (61), 190.1 (11), 191.1 (29), 193.1 (46), 194.1 (60), 197.1 (13), 198.1 (22), 282.1 (65), 283.2 (20), 338.2 (13).

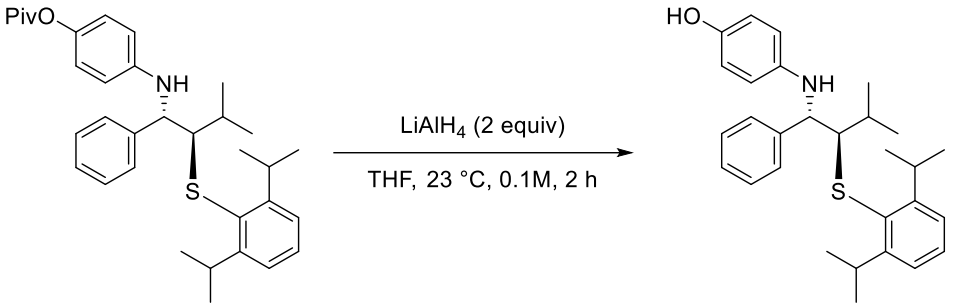
TLC: R_f 0.24 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ +115.9 (*c* = 1.04, $CHCl_3$)

HPLC: t_R 37.5 min (93.0%); t_R 42.1 min (7.0%) (Supelco Astec, hexanes/*i*-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C) [Determined with derivative **32c**]

Analysis:	$C_{34}H_{45}NO_2S$	(531.79)		
	Calcd:	C, 76.79%;	H, 8.53%;	N, 2.63%
	Found:	C, 76.88%;	H, 8.81%;	N, 2.87%

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-3-methyl-1-phenylbutyl)amino)phenol (32c)



(1*S*, 2*R*)-**32** (1*S*, 2*R*)-**32c**

An oven-dried, 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*,2*R*)-**32** (10 mg, 0.018 mmol), THF (0.30 mL) and cooled to 0 °C in an ice/water bath. Lithium Aluminum Hydride (2.0 mg, 0.037 mmol, 2.0 equiv) was added in a single portion. Full conversion was observed by TLC (hexanes/EtOAc, 5:1). The reaction mixture was quenched with methanol (0.2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (1 x 2 mL) and the reaction mixture further diluted with EtOAc (3 mL) and 50% brine (5 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (1 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (0.5 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **32c**. The product was chromatographed (6 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 6 mg (71%) of **32c** as a white solid.

Data for **32c**:

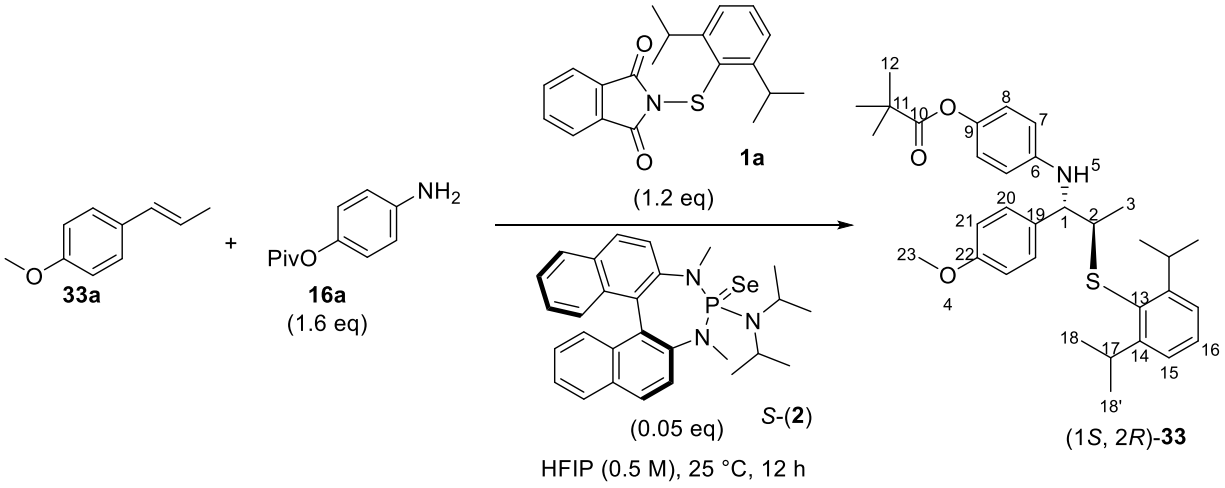
^{1}H NMR: (500 MHz, $CDCl_3$)

7.34 (t, J = 7.7 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.25 – 7.18 (m, 1H), 7.17 – 7.11 (m, 4H), 6.58 (d, J = 8.7 Hz, 2H), 6.31 (d, J = 8.7 Hz, 2H), 4.53 (d, J = 1.9 Hz, 1H), 4.14 (s, 1H), 4.00 – 3.97 (m, 1H), 3.80 (br s, 2H), 3.11 (dd, J = 3.8, 2.3 Hz, 1H), 2.02 (pd, J = 6.9, 2.3 Hz, 1H), 1.28 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.7 Hz, 6H), 1.08 (d, J = 6.8 Hz, 3H), 0.93 (s, 6H).

HRMS: (EI, 70 eV)

Calcd for $C_{29}H_{37}NOS$ ($[M]^+$): 447.2596, Found: 447.2617

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-3-methyl-1-phenylbutyl)amino)phenyl Pivalate (33)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene **33a** (148 mg, 1.0 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16b** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over

anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**33**. The product was chromatographed (75 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford 434 mg (81%) of (+)-**33** as a viscus yellow oil. The product was further purified by Kugelrohr distillation (140 °C, 3.4 x 10^{-5} mm Hg) to afford 395 mg (74%) of (+)-**33** as a yellow solid.

Data for (+)-**33**:

m.p.: 62–64 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.35 (t, J = 7.7 Hz, 1H, HC(15)), 7.19 (d, J = 7.7 Hz, 2H, HC(14)), 7.12 (d, J = 8.6 Hz, 2H, HC(20)), 6.84 (d, J = 8.7 Hz, 2H, HC(19)), 6.77 (d, J = 8.9 Hz, 2H, HC(7)), 6.46 (d, J = 8.9 Hz, 2H, HC(6)), 4.52 (br s, 1H, HN(4)), 4.15 (t, J = 2.5 Hz, 1H, HC(1)), 3.89 – 3.81 (m, 2H, HC(2)), 3.79 (s, 3H, H_3C(22)), 3.21 (qd, J = 7.2, 3.1 Hz, 1H, HC(2)), 1.34 (s, 9H, H_3C(11)), 1.23 (d, J = 6.8 Hz, 6H, H_3C(17')), 1.19 (d, J = 7.2 Hz, 3H, H_3C(3)), 1.07 (d, J = 6.8 Hz, 6H, H_3C(17)).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.7 (C(9)), 158.8 (C(21)), 153.8 (C(13)), 145.5 (C(8)), 142.8 (C(5)), 132.8 (C(18)), 130.1 (C(12)), 129.6 (HC(15)), 128.1 (HC(20)), 123.8 (HC(14)), 121.8 (HC(7)), 114.5 (HC(6)), 114.0 (HC(19)), 60.0 (HC(1)), 55.3 (HC(22)), 52.7 (HC(2)), 39.0 (C(10)), 31.7 (HC(16)), 27.3 (H_3C(11)), 24.9 (H_3C(17')), 24.1 (H_3C(17)), 14.1 (H_3C(3)).

IR: (neat)

2964 (m), 2869 (w), 1747 (m), 1611 (w), 1584 (w), 1510 (s), 1480 (w), 1462 (w), 1420 (w), 1396 (w), 1362 (w), 1302 (w), 1278 (w), 1248 (m), 1198 (m), 1167 (m), 1122 (s), 1033 (w), 928 (w), 889 (w), 834 (w), 802 (w), 749 (w), 520 (w).

LRMS: (EI, 70 eV)

109.1 (48), 147.1 (12), 148.1 (24), 149.0 (25), 177.1 (15), 179.1 (12), 193.1 (11), 219.1 (32), 227.1 (10), 312.2 (100), 313.2 (19), 340.2 (21).

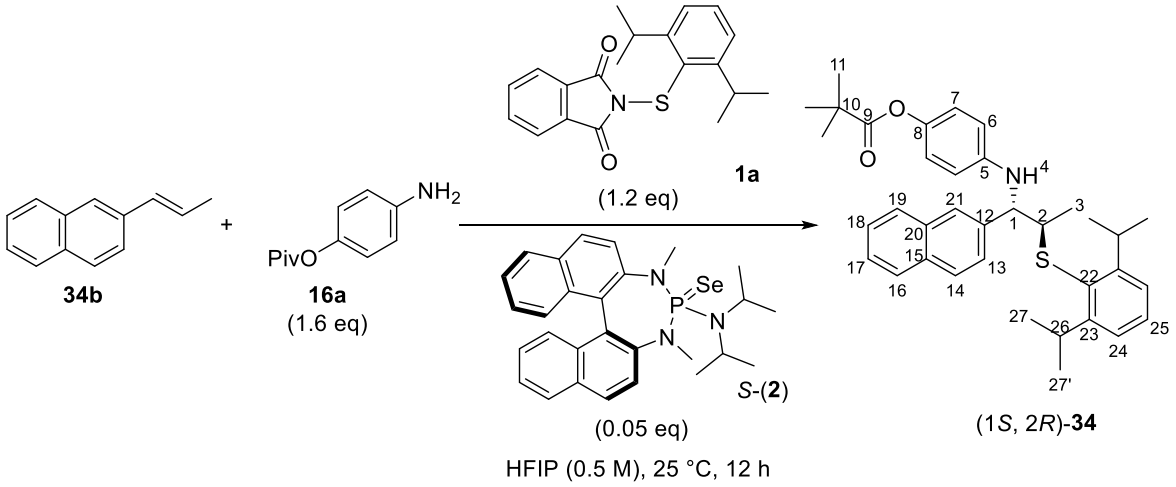
TLC: R_f 0.32 (silica gel, hexanes/EtOAc, 9:1, UV)

Opt. Rot.: $[\alpha]_D^{24}$ +53.3 (c = 1.35, $CHCl_3$)

SFC: t_R 11.2 min (4.8%); t_R 14.5 min (95.2%) (Chiralcel OD, gradient 5% MeOH/CO_2 to 20% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C)

Analysis:	$C_{33}H_{43}NO_3S$	(533.77)		
	Calcd:	C, 74.26%;	H, 8.12%;	N, 2.62%
	Found:	C, 74.61%;	H, 8.42%;	N, 2.81%

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-(naphthalen-2-yl)propyl)amino)phenyl Pivalate (34)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *(E)*-2-(prop-1-en-1-yl)naphthalene **34b** (168 mg, 1.0 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16b** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)-**2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 24:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**34**. The product was chromatographed (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 482 mg (87%) of (+)-**34** as an impure, yellow-orange solid. (+)-**34** was chromatographed a second time (18 g silica gel, 2 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) to afford 472 mg

(85%) of (+)-**34** as an off white foam. Recrystallization from boiling ethanol (3 mL) provided 416 mg (75%) of analytically pure (+)-**34** as white needles.

Data for (+)-**34**:

m.p.: 112–114 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.85 – 7.74 (m, 3H, HC(13), HC(18) and HC(19)), 7.74 – 7.67 (m, 1H, HC(21)), 7.49 – 7.42 (m, 2H, HC(17) and HC(16)), 7.38 (t, *J* = 7.7 Hz, 1H, HC(25)), 7.31 – 7.26 (m, 1H, HC(14)), 7.21 (d, *J* = 7.7 Hz, 2H, HC(24)), 6.78 – 6.71 (m, 2H, HC(7)), 6.53 – 6.43 (m, 2H, HC(6)), 4.63 (d, *J* = 2.7 Hz, 1H, HN(4)), 4.33 (t, *J* = 2.9 Hz, 1H, HC(1)), 3.84 (hept, *J* = 6.9 Hz, 2H, HC(26)), 3.34 (qd, *J* = 7.2, 3.1 Hz, 1H, HC(2)), 1.32 (s, 9H, H_3C(11)), 1.24 (d, *J* = 7.0 Hz, 6H, H_3C(27')), 1.21 (d, *J* = 7.2 Hz, 3H, H_3C(3)), 1.07 (d, *J* = 6.8 Hz, 6H, H_3C(27)).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.5 (C(9)), 153.7 (C(23)), 145.4 (C(5)), 142.8 (C(8)), 138.4 (C(12)), 133.4 (C(15)), 132.8 (C(20)), 129.9 (C(22)), 129.5 (HC(25)), 128.3 (HC(18)), 127.9 (HC(13)), 127.6 (HC(19)), 126.1 (HC(17)), 125.8 (HC(16)), 125.7 (HC(21)), 125.0 (HC(14)), 123.8 (HC(24)), 121.7 (HC(7)), 114.4 (HC(6)), 60.6 (HC(1)), 52.5 (HC(2)), 38.9 (C(10)), 31.6 (HC(26)), 27.2 (H_3C(11)), 24.8 (H_3C(27')), 24.0 (H_3C(27)), 14.0 (H_3C(3)).

IR: (neat)

3374 (w), 2963 (w), 1744 (m), 1607 (w), 1515 (m), 1461 (w), 1396 (w), 1362 (w), 1320 (w), 1304 (w), 1277 (w), 1196 (m), 1167 (m), 1113 (s), 1051 (w), 1027 (w), 929 (w), 887 (w), 857 (w), 824 (s), 803 (m), 773 (w), 747 (m), 660 (w), 582 (w), 560 (w), 528 (w), 515 (m), 482 (m).

LRMS: (EI, 70 eV)

55.1 (23), 57.1 (44), 67.1 (11), 69.1 (20), 70.1 (10), 71.1 (17), 77.0 (36), 81.1 (12), 83.1 (17), 85.1 (13), 91.1 (17), 95.1 (10), 97.1 (15), 105.0 (74), 109.1 (51), 111.1 (10), 115.1 (15), 128.1 (11), 135.0 (11), 137.0 (14), 149.1 (100), 150.1 (12), 151.1 (13), 163.1 (17), 165.1 (12), 167.1 (15), 168.1 (14), 179.1 (24), 193.1 (16), 194.1 (18), 219.1 (15), 300.1 (22), 332.2 (58), 333.2 (14).

TLC: R_f 0.22 (silica gel, hexanes/EtOAc, 24:1, UV/CAM)

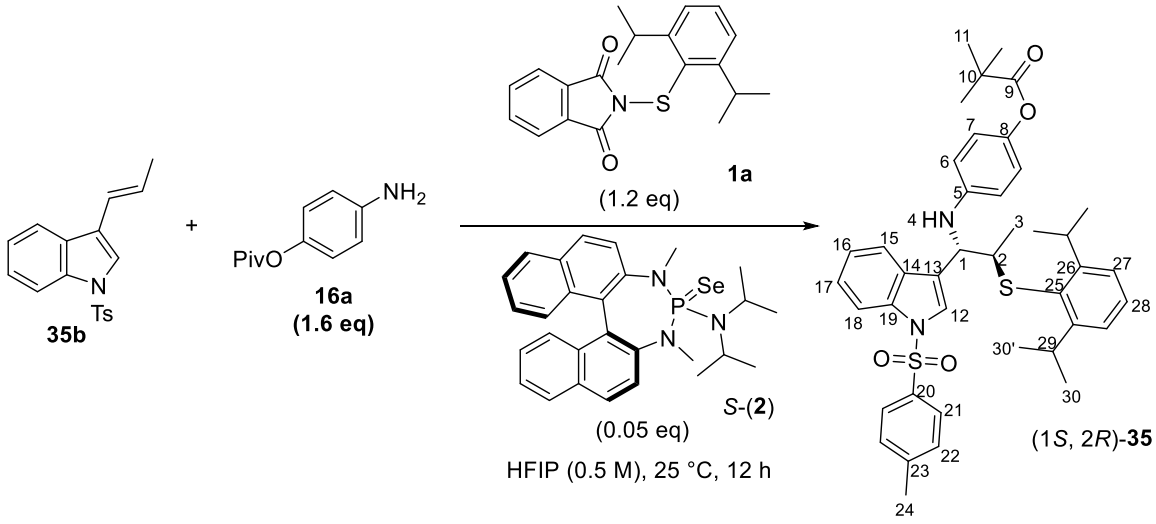
Opt. Rot.: $[\alpha]_D^{24}$ +56.8 (c = 1.06, $CHCl_3$)

SFC: t_R 25.9 min (3.7%); t_R 32.5 min (96.2%) (Chiralcel AD, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 over 15 min, 2.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{36}H_{43}NO_2S$ (553.80)

Calcd:	C, 78.08%;	H, 7.83%;	N, 2.53%
Found:	C, 78.00%;	H, 8.10%;	N, 2.74%

Preparation of 4-(((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-(1-tosyl-1H-indol-3-yl)propyl)amino)phenyl Pivalate (35)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with 1-methyl-*(E)*-3-(prop-1-en-1-yl)-1-tosyl-1H-indole **35b** (311 mg, 1.0 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16a** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407.0 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26.0 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The flask was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**35**. The product was chromatographed (66 g silica gel, 3.5 cm column, dry load

on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 19:1) to afford 572 mg (82%) of (+)-**35** as a tan foam. The product recrystallized from diethyl ether (5 mL) to afford 523 mg (76%) of (+)-**35** as white crystals.

Data for (+)-**35**:

m.p.: 102–105 °C (Et_2O)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.99 (dd, *J* = 8.4, 1.1 Hz, 1H, HC(18)), 7.53 (d, *J* = 8.3 Hz, 2H, HC(22)), 7.48 (s, 1H, HC(12)), 7.39 (t, *J* = 7.7 Hz, 1H, HC(28)), 7.33 – 7.26 (m, 1H, HC(17)), 7.21 (d, *J* = 7.7 Hz, 2H, HC(27)), 7.13 (d, *J* = 8.4 Hz, 2H, HC(21)), 7.09 (td, *J* = 7.6, 1.0 Hz, 1H, HC(16)), 6.75 – 6.65 (m, 3H, HC(15) and HC(7)), 6.40 (d, *J* = 8.9 Hz, 2H, HC(6)), 4.44 (d, *J* = 2.9 Hz, 1H, HN(4)), 4.41 (d, *J* = 2.9 Hz, 1H, HC(1)), 3.77 (h, *J* = 6.6 Hz, 2H, HC(29)), 3.28 (qd, *J* = 7.1, 2.6 Hz, 1H, HC(2)), 2.32 (s, 3H, H_3C(24)), 1.37 (s, 9H, H_3C(11)), 1.28 (d, *J* = 7.2 Hz, 3H, H_3C(3)), 1.18 (d, *J* = 6.8 Hz, 6H, H_3C(30')), 1.03 (d, *J* = 5.6 Hz, 6H, H_3C(30)).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.5 (C(9)), 153.8 (C(26)), 144.9 (C(8)), 144.6 (C(23)), 143.0 (C(5)), 135.9 (C(14)), 134.7 (C(20)), 130.2 (C(25)), 129.8 (HC(21)), 129.7 (HC(28)), 128.9 (C(19)), 126.7 (HC(22)), 125.3 (HC(12)), 124.8 (HC(17)), 123.6 (HC(27)), 123.2 (HC(16)), 121.9 (C(13)), 121.7 (HC(7)), 118.9 (HC(15)), 114.5 (HC(6)), 114.2 (HC(18)), 53.2 (HC(1)), 49.8 (HC(2)), 39.0 (C(10)), 31.6 (HC(29)), 27.2 (H_3C(11)), 24.6 (H_3C(30')), 24.0 (H_3C(30)), 21.5 (H_3C(24)), 14.2 (H_3C(3)).

IR: (neat)

2963 (w), 1744 (m), 1598 (w), 1509 (s), 1447 (m), 1364 (m), 1277 (m), 1198 (m), 1173 (s), 1118 (s), 1054 (w), 1030 (w), 967 (m), 888 (w), 835 (w), 800 (m), 746 (s), 704 (m), 663 (m), 592 (m), 571 (s), 537 (s).

LRMS: (EI, 70 eV)

55.1 (11), 57.1 (42), 65.0 (20), 77.0 (19), 80.1 (19), 91.1 (68), 105.0 (12), 108.0 (16), 109.1 (90), 115.1 (24), 117.1 (18), 127.1 (14), 128.1 (35), 129.1 (33), 130.1 (13), 134.0 (10), 135.0 (17), 137.0 (21), 149.0 (58), 151.1 (11), 154.1 (20), 155.0 (13), 156.1 (100), 157.1 (20), 163.1 (19), 175.1 (16), 177.1 (10), 179.1 (34), 191.1 (17), 193.1 (28), 194.1 (28), 219.1 (18), 235.1 (11), 311.1 (36), 312.1 (14), 348.2 (19), 349.2 (11), 475.2 (56), 476.2 (17), 503.2 (37), 504.2 (13).

TLC: R_f 0.52 (silica gel, hexanes/EtOAc, 4:1, UV/CAM)

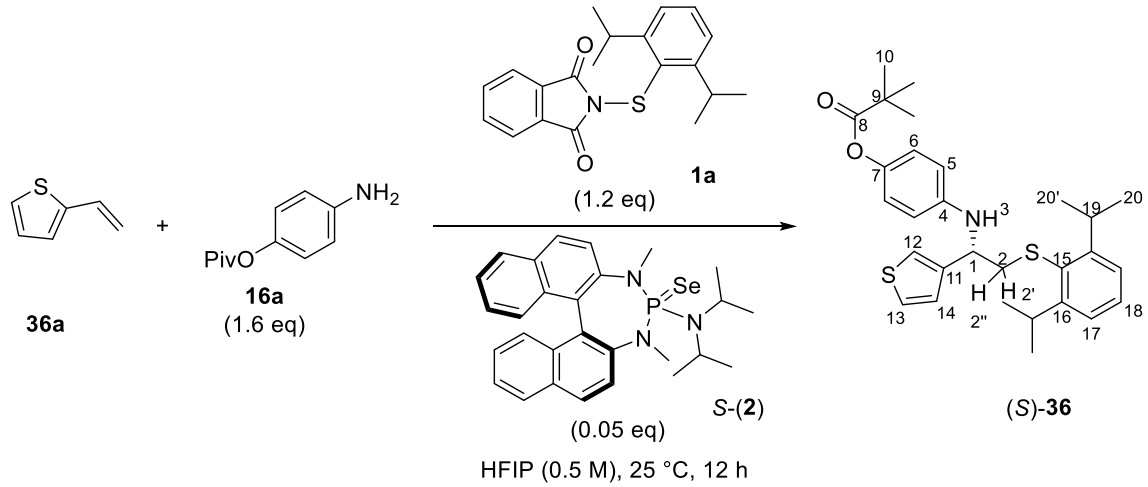
Opt. Rot.: $[\alpha]_D^{24}$ +156.2 (c = 1.46, $CHCl_3$)

SFC: t_R 11.2 min (4.7%); t_R 15.7 min (95.3%) (Chiralpak OD, MeOH/CO_2, Gradient 5% MeOH/CO_2 to 20% MeOH/CO_2 over 10 min; 20% MeOH/CO_2 2.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{41}H_{48}N_2O_4S$ (696.96)

Calcd:	C, 70.66%;	H, 6.94%;	N, 4.02%
Found:	C, 71.00%;	H, 7.14%;	N, 4.08%

Preparation of (*S*)-4-((2-((2,6-Diisopropylphenyl)thio)-1-(thiophen-3-yl)ethyl)amino)phenyl Pivalate (36)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with 3-vinylthiophene **36a** (110.0 mg), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16a** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous,

yellow solution resulted. Catalyst (*S*)- **2** (26 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 23 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 12:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL separatory funnel. The vial was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**36**. The product was purified by chromatography (30 g silica gel, 2 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 386 mg (78%) of (+)-**36** as a yellow foam. The product was purified by trituration as follows. The crude material was suspended in methanol (2 mL) and sonicated at 23 °C and cooled to -20 °C for 12 h. Vacuum filtration of this suspension yielded 337 mg (68%) of analytically pure (+)-**36** as a fine, off white powder.

Data for (+)-**36**:

m.p.: 69–70 °C (methanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.32 (t, *J* = 7.7 Hz, 1H, HC(18)), 7.28 – 7.26 (m, 1H, HC(14)), 7.18 – 7.17 (m, 1H, HC(13)), 7.15 (d, *J* = 7.7 Hz, 2H, HC(17)), 6.99 (dd, *J* = 5.0, 1.3 Hz, 1H, HC(12)), 6.82 – 6.71 (m, 2H, HC(6)), 6.47 – 6.40 (m, 2H, HC(5)), 4.46 – 4.37 (m, 1H, HC(1)), 4.33 (s, 1H, NH(3)), 3.83 (hept, *J* = 6.9 Hz, 2H, HC(19)), 3.06 (dd, *J* = 13.3, 4.8 Hz, 1H, $H_2C(2')$), 3.00 (dd, *J* = 13.2, 8.2 Hz, 1H, $H_2C(2'')$), 1.32 (s, 9H, $H_3C(10)$), 1.19 (d, *J* = 6.8 Hz, 6H, $H_3C(20')$), 1.13 (d, *J* = 6.8 Hz, 6H, $H_3C(20)$)).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.7 (C(8)), 153.5 (C(16)), 145.0 (C(7)), 143.8 (C(11)), 143.0 (C(4)), 130.7 (C(15)), 129.6 (HC(18)), 126.5 (HC(11)), 126.1 (HC(12)), 123.9 (HC(17)), 122.0 (HC(6)), 121.5 (HC(13)), 114.1 (HC(5)), 54.4 (HC(1)), 44.8 ($H_2C(2)$), 39.1 (C(9)), 31.8 (HC(19)), 27.3 ($H_3C(10)$), 24.7 ($H_3C(20')$), 24.4 ($H_3C(20)$).

IR: (neat)

3396 (w), 2963 (m), 2869 (w), 1742 (m), 1612 (w), 1574 (w), 1509 (s), 1478 (m), 1461 (m), 1396 (w), 1384 (w), 1362 (w), 1279 (m), 1197 (s), 1166 (m), 1120 (s), 1053 (w), 1029 (w), 908 (m), 889 (w), 838 (m), 797 (m), 777 (w), 730 (s), 686 (w), 648 (m), 630 (w), 542 (w), 519 (m).

LRMS: (EI, 70 eV)

57.1 (13), 97.0 (11), 105.0 (13), 109.1 (33), 149.0 (68), 163.1 (20), 191.1 (10), 192.1 (12), 193.1 (11), 204.0 (11), 288.1 (100), 289.1 (17), 302.1 (27).

TLC: R_f 0.55 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

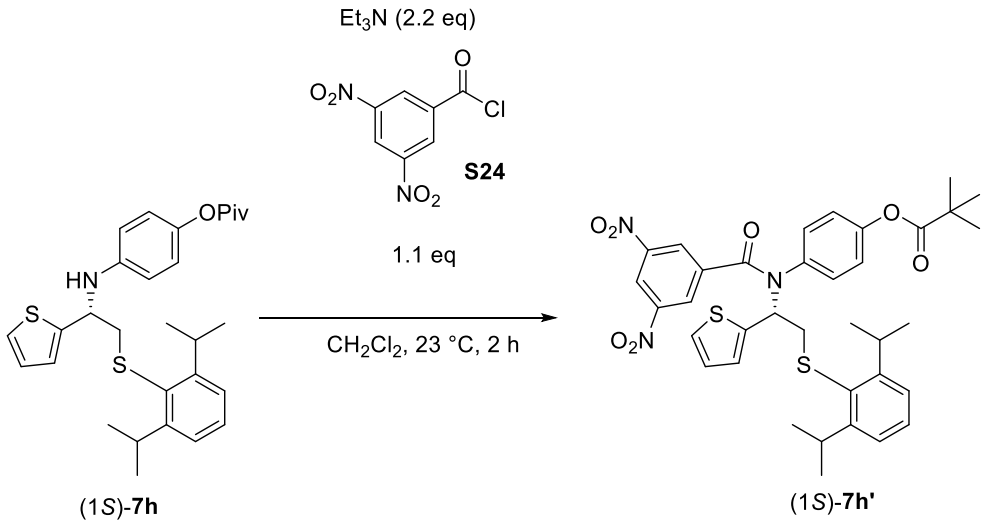
Opt. Rot.: $[\alpha]_D^{24}$ +56.6 (c = 1.15, $CHCl_3$)

SFC: t_R 26.0 min (88.3%); t_R 29.1 min (11.7%) (Regis (*R*,*R*)-Whelk O1, CO_2/MeOH, 90:10, 2.5 mL/min, 220 nm, 24 °C) [Determined with derivative **36b**]

Analysis: $C_{29}H_{37}NO_2S_2$ (495.74)

Calcd:	C, 70.26%;	H, 7.52%;	N, 2.83%
Found:	C, 70.36%;	H, 7.65%;	N, 3.02%

Preparation of (*S*)-4-(*N*-(2-((2,6-Diisopropylphenyl)thio)-1-(thiophen-3-yl)ethyl)-3,5-dinitrobenzamido)phenyl Pivalate (36b)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**36** (15.0 mg, 0.034 mmol), CH_2Cl_2 (300 μL), Et_3N (11 μL, 0.076 mmol, 2.2 equiv) and 3,5-

dinitrobenzoyl chloride (9 mg, 0.04 mmol, 1.1 equiv) and the mixture was stirred at 23 °C for 2 h. A homogeneous, yellow solution resulted which slowly formed a precipitate over the course of the reaction. Full conversion was observed by TLC (hexanes/EtOAc, 9:1). The reaction mixture was diluted with CH_2Cl_2 (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with CH_2Cl_2 (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **36b**. The product was purified by chromatography (6 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 16 mg (74%) of **36b** as a white solid.

Data for **36b**:

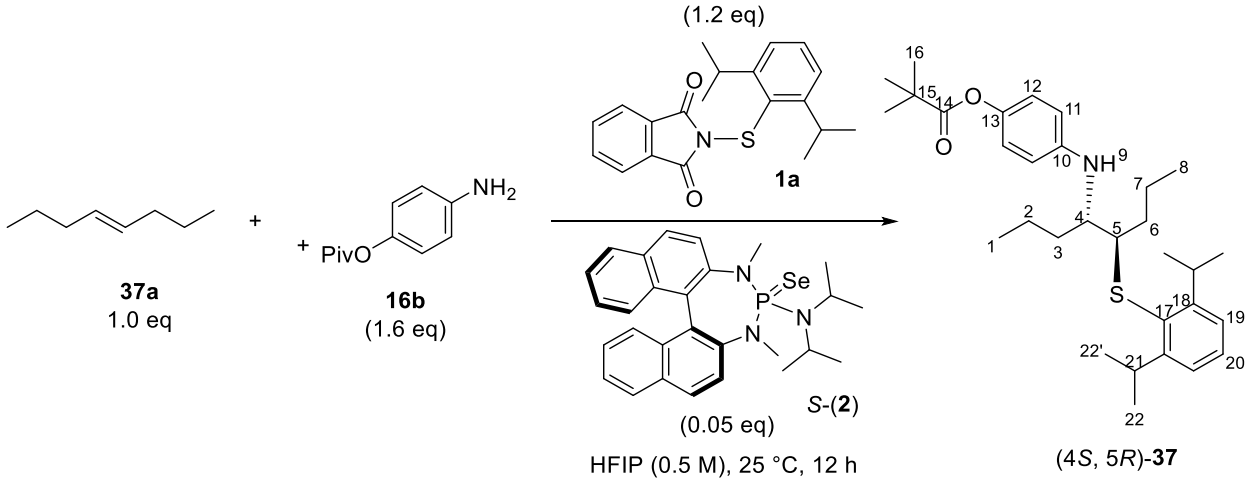
^{1}H NMR: (500 MHz, DMSO-d_6, 80°C)

8.71 – 8.66 (m, 1H), 8.43 (d, J = 2.3 Hz, 2H), 7.47 (dd, J = 5.0, 2.9 Hz, 1H), 7.34 (dd, J = 14.8, 7.0 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 7.09 – 7.03 (m, 1H), 7.01 (s, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.04 (s, 1H), 3.82 (p, J = 6.9 Hz, 2H), 3.43 (dd, J = 12.4, 6.8 Hz, 1H), 3.30 (dd, J = 12.3, 8.6 Hz, 1H), 1.23 (s,9), 1.18 (dd, J = 6.9, 2.4 Hz, 12H).

HRMS: (EI, 70 eV)

Calcd for $C_{36}H_{39}N_3O_5S$ ($[M]^+$): 689.2229, Found: 689.2215

Preparation of 4-(((4*S*,5*R*)-5-((2,6-Diisopropylphenyl)thio)octan-4-yl)amino)phenyl pivalate (37)



A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with *trans*-4-octene **37a** (112.0 mg, 1.00 mmol), hexafluoroisopropyl alcohol (2 mL), 4-aminophenyl pivalate **16a** (309 mg, 1.60 mmol, 1.60 equiv) and **1a** (407 mg, 1.20 mmol, 1.20 equiv). A homogeneous, yellow solution resulted. Catalyst (*S*)- **2** (26 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was stirred at 25 °C for 12 h. Full conversion was observed by TLC (hexanes/EtOAc, 24:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 125-mL seperatory funnel. The vial was rinsed with EtOAc (2 x 3 mL) and the reaction mixture further diluted with EtOAc (20 mL) and 50% brine (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (-)-**37**. The product was purified by chromatography (66 g silica gel, 3 cm column, dry load on Celite, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) to afford 344 mg (79%) of (-)-**37** as a thick, viscus, yellow oil. Attempts at vacuum distillation resulted in partial decomposition of the product.

Data for (-)-**37**:

b.p.: 185 °C (3.4×10^{-5} Torr, partial decomposition)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.18 (t, J = 7.2 Hz, 1H, HC(20)), 7.02 (d, J = 7.7 Hz, 2H. HC(19)), 6.73 (d, J = 8.8 Hz, 2H, HC(12)), 6.34 (d, J = 8.3 Hz, 2H, HC(11)), 3.73 (hept, J = 6.8 Hz, 2H, HC(21)), 3.51 (dt, J = 9.6, 3.1 Hz, 1H, HC(4)), 3.07 (ddd, J = 8.5, 5.7, 2.6 Hz, 1H, HC(5)), 1.71 – 1.28 (m, 6H, $H_2C(2'')$, $H_2C(3)$, $H_2C(6)$, $H_2C(7'')$), 1.26 (s, 9H, $H_3C(16)$), 1.24 – 1.10 (m, 2H, $H_2C(2')$ and $H_2C(7')$), 1.05 (d, J = 6.8 Hz, 6H, $H_3C(22')$), 0.92 (d, J = 6.9 Hz, 6H, $H_3C(22)$), 0.87 (t, J = 7.3 Hz, 3H, $H_3C(1)$), 0.76 (t, J = 7.2 Hz, 3H, $H_3C(8)$).

^{13}C NMR: (126 MHz, $CDCl_3$)

177.6 (C(14)), 153.5 (C(18)), 145.3 (C(13)), 142.2 (C(10)), 130.4 (C(17)), 128.8 HC(20)), 123.7 (HC(19)), 122.1 (HC(12)), 113.3 HC(11)), 55.2 (HC(4)), 54.7 (HC(5)), 39.0 (C(15)), 35.3 (HC(6)), 31.9 (HC(3)), 31.3 (HC(21)), 27.2 ($H_3C(16)$), 24.3 ($H_3C(22)$), 24.1 ($H_3C(22')$), 20.9 ($H_2C(7)$), 20.1 ($H_2C(2)$), 14.09 ($H_3C(1)$), 14.07 ($H_3C(8)$).

IR: (neat)

3384 (w), 2962 (m), 1728 (m), 1614 (w), 1515 (s), 1480 (m), 1459 (m), 1394 (w), 1362 (w), 1320 (w), 1282 (m), 1197 (s), 1167 (m), 1127 (s), 1030 (m), 931 (w), 888 (w), 839 (w), 823 (w), 799 (m), 755 (s), 745 (m), 732 (m), 699 (w), 625 (w), 516 (m), 455 (m).

LRMS: (EI, 70 eV)

55.1 (17), 57.1 (38), 69.1 (43), 81.1 (11), 105.0 (11), 109.1 (34), 111.1 (22), 123.0 (16), 135.0 (18), 137.0 (16), 149.0 (49), 151.1 (39), 163.1 (20), 164.1 (22), 179.1 (32), 193.1 (21), 194.1 (67), 247.2 (22), 248.2 (100), 249.2 (25), 261.2 (16), 304.2 (29).

HRMS: (EI, 70 eV)

Calcd for $C_{31}H_{37}NO_2S$ ($[M]^+$): 497.3328, Found: 497.3342

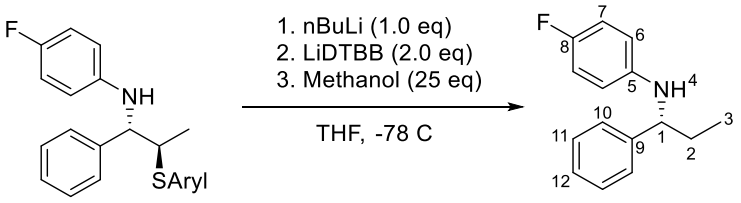
TLC: R_f 0.43 (silica gel, Hexanes/EtOAc, 9:1, UV/CAM)

Opt. Rot.: $[\alpha]_D^{24}$ -129.3 (c = 1.09 in $CHCl_3$)

SFC: t_R 10.5 min (95.1%); t_R 11.8 min (4.9%) (Chiralpak IB-3, Hexanes/9:1 Hexanes:*i*PrOH, 90:10, 1.0 mL/min, 220 nm, 24 °C)

Product Manipulations

Preparation of (*R*)-4-Fluoro-*N*-(1-phenylpropyl)aniline (63)



(1*S*, 2*R*)-**13** (*R*)-**63**

To an oven-dried, 25-mL Schlenk flask fitted with a Teflon stir bar, internal digital thermometer and a rubber septum was charged (1*S*, 2*R*)-**13** (422 mg, 1.00 mmol) and THF (10 mL). The solution was cooled to an internal temperature of 2 °C (ice/water bath). *n*-BuLi (430 μL, 2.3 M, 1.00 mmol, 1.0 equiv) was added dropwise via syringe over 5 min. During the course of the addition the internal temperature rose to 5 °C. The reaction was stirred at 0 °C for 20 min and subsequently cooled to an internal temperature of -72 °C (dry ice/*i*-PrOH) bath. Preformed LiDTBB (2.2 mL, 0.9M, 2.0 equiv, 2.0 mmol) was dropwise added to the reaction mixture over 10 min maintaining the internal temperature below -65 °C. During addition the reaction became amber and upon complete addition the reaction was dark green . The mixture was stirred at -78 °C for an additional 2 min at which time methanol (1.0 mL, 25 equiv, 25 mmol) was added dropwise over approximately 15 sec. The mixture became colorless. The mixture was warmed to 23 °C and diluted with ether (5 mL), decanted into a 120-mL separatory funnel, and further diluted with ether (5 mL) and brine (10 mL). The organics were removed and the aqueous layer extracted with ether (3 x 25 ml). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (-)-**63** as a white solid. Purification by column chromatography (27 g silica gel, 2 cm column, 10-mL fractions, isocratic hexanes/EtOAc, 49:1) afforded 209 mg (91%) of (-)-**63** as a clear oil. Further purification via Kugelrohr distillation (100 °C, 0.2 mm Hg) provided 199 mg (87%) of analytically pure (-)-**63** as clear oil.

Data for (-)-**63**:

b.p.: 100 °C (200 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.31 (d, *J* = 4.4 Hz, 4H, HC(10) and HC(11)), 7.23 (dt, *J* = 8.6, 4.3 Hz, 1H, HC(12)), 6.84 – 6.69 (m, 2H, HC(7)), 6.51 – 6.36 (m, 2H, HC(6)), 4.15 (t, *J* = 6.6 Hz, 1H, HC(1)), 3.97 (s, 1H, HN(4)), 1.82 (dtd, *J* = 17.5, 13.8, 6.8 Hz, 2H, H_2C(2)), 0.95 (t, *J* = 7.4 Hz, 3H, H_3C(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

155.61 (d, *J* = 234.5 Hz, 1C, C(8)), 143.85 (C(5)), 143.71 (C(9)), 128.55 (HC(11)), 126.99 (HC(12)), 126.49 (HC(10)), 115.49 (d, *J* = 22.3 Hz, 1C, HC(7)), 114.02 (d, *J* = 7.3 Hz, 1C, HC(6)), 60.37 HC(1)), 31.72 H_2C(2)), 10.82 H_3C(3)).

IR: (neat)

3420 (w), 3029 (w), 2966 (w), 2932 (w), 2875 (w), 1613 (w), 1506 (s), 1452 (m), 1401 (w), 1382 (w), 1358 (w), 1315 (w), 1216 (m), 1156 (w), 1134 (w), 1097 (w), 1074 (w), 1051 (w), 1027 (w), 1008 (w), 906 (w), 858 (w), 816 (s), 790 (m), 772 (m), 750 (m), 699 (s), 629 (w), 508 (m).

LRMS: (EI, 70 eV)

83.0 (23), 84.0 (12), 95.0 (72), 110.0 (13), 111.0 (62), 119.1 (13), 122.0 (83), 152.1 (15), 198.1 (31), 228.1 (12), 229.1 (100), 230.1 (16).

TLC: R_f 0.45 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

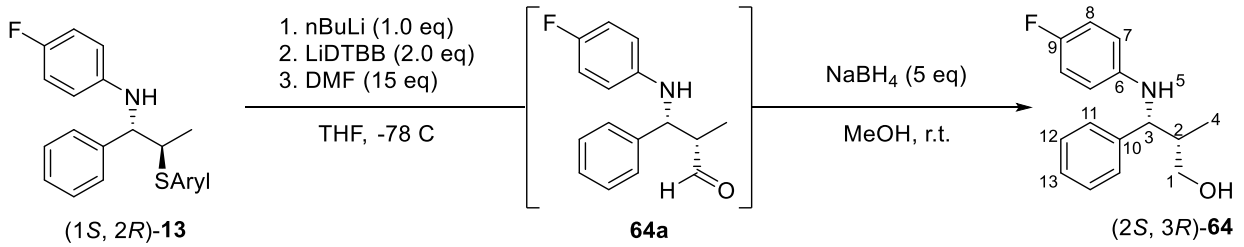
Opt. Rot.: $[\alpha]_D^{24}$ -5.29 (*c* = 1.07, 100% EtOH)

HPLC: t_R 11.43 min (99.2%); t_R 12.43 min (0.8%) (Supelco Astec, hexanes/*i*-PrOH, 95:5, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{15}H_{16}FN$ (229.29)

Calcd:	C, 78.57%;	H, 7.03%;	N, 6.11%
Found:	C, 78.85%;	H, 6.99%;	N, 6.45%

Preparation of (2*S*,3*R*)-3-((4-Fluorophenyl)amino)-2-methyl-3-phenylpropan-1-ol (64)



To an oven-dried, 25-mL Schlenk flask fitted with a Teflon stir bar, internal digital thermometer and a rubber septum was added (1*S*, 2*R*)-**13** (422 mg, 1.00 mmol) and THF (10 mL). The solution was cooled to an internal temperature of 1 °C (ice/water bath). *n*-BuLi (1.0 equiv, 2.3 M, 430 μL, 1.00 mmol, 1.0 equiv) was added dropwise via syringe over 10 min. During the course of the addition the internal temperature rose to 5 °C. The reaction was stirred at 0 °C for 20 min and subsequently cooled to an internal temperature of -72 °C (dry ice/*i*-PrOH) bath. Preformed LiDTBB (2.2 mL, 0.9M, 2.0 equiv, 2.0 mmol) was dropwise added to the reaction mixture over 10 min maintaining the internal temperature below -65 °C. During addition the reaction mixture became amber and upon complete addition the reaction was dark green. The mixture was stirred at -78 °C for an additional 2 min at which time DMF (1.2 mL, 15 equiv, 15 mmol) was added dropwise over approximately 15 sec. The solution turned amber. The mixture was kept in the -78 °C bath for an additional 2 min and subsequently quenched by addition of sat. aq. ammonium chloride solution (1 mL) and warmed to 23 °C. The mixture was diluted with ether (5 mL), decanted into a 120-mL separatory funnel, and further diluted with ether (5 mL) and brine (10 mL). The organics were removed and the aqueous layer extracted with ether (3 x 25 ml). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (5 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg), taking care not to expose the crude material to elevated temperatures, to afford crude **64a** as a white solid.

The crude material was transferred to a 50-mL, round-bottomed flask (2 x 5 mL methanol) containing a Teflon stir bar. The heterogeneous mixture was placed in a 23 °C water bath and sodium borohydride (189 mg, 5.0 mmol, 5 equiv) was added over 1 min. The reaction was stirred at 23 °C for 2 h. TLC analysis (hexanes/EtOAc, 4:1) indicated full consumption of the starting material. The reaction was quenched with water (2 mL) and decanted into a 125-mL separatory funnel and diluted with ether (25 mL) and brine (25 mL). The organics were removed and the aqueous layer extracted with ether (3 x 25 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (4 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) afford crude (-)-**64** as a white solid. Purification by column chromatography (66 g silica gel, 3 cm column, 25-mL fractions, isocratic hexanes/EtOAc, 7:3) afforded 187 mg (72%) of (-)-**64** as a white solid. Sublimation (85 °C, 0.4 mm Hg) afforded 180 mg (70%) of analytically pure (-)-**64** as a white solid.

Data for (-)-**64**:

m.p.: 104–106 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.28 – 7.18 (m, 4H, HC(11) and HC(12)), 7.18 – 7.12 (m, 1H, HC(13)), 6.78 – 6.64 (m, 2H, HC(8)), 6.46 – 6.33 (m, 2H, HC(7)), 4.17 (d, *J* = 7.3 Hz, 1H, HC(3)), 3.67 (dd, *J* = 11.0, 3.7 Hz, 1H, $H_2C(1')$), 3.60 (dd, *J* = 10.9, 6.6 Hz, 1H, $H_2C(1'')$), 2.02 (qdd, *J* = 7.7, 3.7, 1.7 Hz, 1H, HC(2)), 0.81 (d, *J* = 7.0 Hz, 3H, $H_3C(4)$).

^{13}C NMR: (126 MHz, $CDCl_3$)

156.0 (d, *J* = 235.5 Hz, 1C, C(9)), 143.5 (d, *J* = 2.0 Hz, 1C, C(6)), 142.0 (C(10)), 128.5 (HC(12)), 127.2 (HC(13)), 127.0 (HC(11)), 115.5 (d, *J* = 22.3 Hz, 1C, HC(8)), 115.1 (d, *J* = 7.5 Hz, 1C, HC(7)), 66.8 ($H_2C(1)$), 64.1 (HC(3)), 41.3 (HC(2)), 14.7 ($H_3C(4)$) .

IR: (neat)

3381 (w), 3029 (w), 2963 (w), 2880 (w), 1613 (w), 1508 (s), 1453 (w), 1403 (w), 1315 (w), 1217 (m), 1156 (w), 1116 (w), 1071 (w), 1027 (m), 979 (w), 912 (w), 819 (m), 774 (m), 702 (m), 574 (w), 512 (w).

LRMS: (EI, 70 eV)

95.0 (29), 117.1 (24), 118.1 (27), 122.0 (34), 123.0 (13), 198.1 (17), 199.1 (14), 200.1 (100), 201.1 (14), 241.1 (14).

TLC: R_f 0.53 (silica gel, hexanes/EtOAc, 1:1, UV)

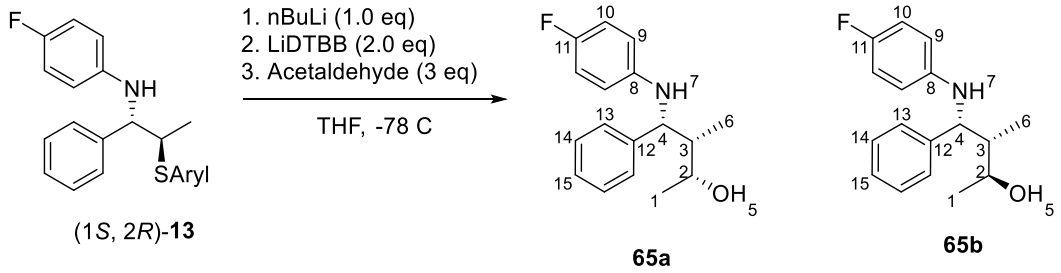
Opt. Rot.: $[\alpha]_D^{24}$ -3.29 (*c* = 1.05, 100% EtOH)

HPLC: t_R 11.55 min (99.8%); t_R 15.08 min (0.2%) (Supelco Astec, hexanes/*i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{16}H_{18}FNO$ (259.32)

Calcd:	C, 74.11%;	H, 7.00%;	N, 5.40%
Found:	C, 74.25%;	H, 7.05%;	N, 5.45%

Preparation of (2R,3S,4R)-4-((4-Fluorophenyl)amino)-3-methyl-4-phenylbutan-2-ol (65a) and (2S,3S,4R)-4-((4-Fluorophenyl)amino)-3-methyl-4-phenylbutan-2-ol (65b)



To an oven-dried, 25-mL Schlenk flask fitted with a Teflon stir bar, internal digital thermometer and a rubber septum was added (1*S*, 2*R*)-**13** (422 mg, 1.00 mmol) and THF (10 mL). The solution was cooled to an internal temperature of 2 °C (ice/water bath). *n*-BuLi (430 μL, 2.3 M, 1.00 mmol, 1.0 equiv) was added dropwise via syringe over 10 min. During the course of the addition the internal temperature rose to 5 °C. The reaction was stirred at 0 °C for 20 min and subsequently cooled to an internal temperature of -70 °C (dry ice/*i*-PrOH) bath. Preformed LiDTBB (2.2 mL, 0.9M, 2.0 equiv, 2.0 mmol) was dropwise added to the reaction mixture over 10 min maintaining the internal temperature below -68 °C. During addition reaction became amber and upon complete addition the reaction was dark green. The mixture was stirred at -78 °C for an additional 2 min at which time acetaldehyde (132 mg, 3 equiv, 3 mmol) in THF (0.5 mL) was added dropwise over approximately 15 sec. The mixture became colorless. The reaction mixture was warmed to 23 °C and quenched with sat. aq. ammonium chloride solution (1 mL). The mixture was diluted with ether (5 mL), decanted into a 120-mL separatory funnel, and further diluted with ether (5 mL) and brine (10 mL). The organic phase was removed and the aqueous layer extracted with ether (2 x 20 ml). The combined organics were dried over anhydrous Na_2SO_4 (5 g), filtered, and concentrated under reduced pressure (15 mm Hg, 23 °C) to afford crude **65a** and **65b** as a white solid. The diastereomers are separable by column chromatography. Purification by column chromatography (30 g silica gel, 2 cm column, 10-mL fractions, isocratic hexanes/EtOAc, 9:1) afforded 120 mg (44%) of **65a** as a clear oil that solidified to a white solid on standing and 117 mg (43%) of **65b** as a clear oil that solidified to a white solid on standing. Analytically pure samples of both diastereomers were prepared from sublimation. Sublimation (105 °C, 0.4 mm Hg) of isomer **65a** afforded 108 mg (40%) of analytically pure **65a** as a white solid. Sublimation (80 °C, 0.4 mm Hg) of isomer **65b** afforded 113 mg (41%) of analytically pure **65b** as a white solid.

Data for (-)-**65a**:

m.p.: 114–115 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.29 (dd, *J* = 8.0, 6.9 Hz, 2H, HC(14)), 7.26 – 7.19 (m, 3H, HC(13) and HC(15)), 6.83 – 6.75 (m, 2H, HC(10)), 6.54 (ddd, *J* = 6.5, 5.2, 2.9 Hz, 2H, HC(9)), 4.31 (dd, *J* = 7.9, 1.1 Hz, 1H, HC(4)), 3.88 (br s, 2H, HO(5) and HN(7)), 3.94 – 3.78 (m, 1H, HC(2)), 1.91 (h, *J* = 7.3 Hz, 1H, HC(3)), 1.24 (d, *J* = 6.2 Hz, 3H, H_3C(6)), 0.68 (d, *J* = 6.9 Hz, 3H, H_3C(1)).

^{13}C NMR: (126 MHz, $CDCl_3$)

156.7 (d, *J* = 236.7 Hz, C(11)), 143.1 (d, *J* = 2.0 Hz, C(8)), 141.6 (C(12)), 128.6 (HC(14)), 127.4 (HC(13) and HC(15)), 116.5 (d, *J* = 7.5 Hz, HC(9)), 115.7 (d, *J* = 22.3 Hz, HC(10)), 71.92(HC(2)), 64.5 (HC(4)), 46.1 (HC(3)), 21.9 (H_3C(6)), 13.7 (H_3C(1)).

^{19}F NMR: (471 MHz, $CDCl_3$)

-126.12 (tt, *J* = 8.7, 4.5 Hz).

IR: (neat)

3367 (w), 3030 (w), 2973 (w), 2928 (w), 1613 (w), 1508 (s), 1453 (w), 1383 (w), 1313 (w), 1261 (w), 1217 (m), 1156 (w), 1121 (w), 1094 (w), 1050 (w), 1029 (w), 969 (w), 936 (w), 910 (w), 819 (m), 770 (m), 733 (w), 702 (m), 526 (w).

LRMS: (EI, 70 eV)

91.1 (22), 95.0 (30), 111.1 (17), 117.1 (14), 122.0 (39), 198.1 (16), 199.1 (12), 200.1 (100), 201.1 (52), 273.2 (20).

TLC: R_f 0.52 (silica gel, hexanes/EtOAc, 1:1, UV)

Opt. Rot.: $[\alpha]_D^{24}$ -7.41 (*c* = 1.34, 100% EtOH)

HPLC: t_R 10.9 min (99.6%); t_R 19.2 min (0.4%) (Supelco Astec, hexanes/*i*PrOH, 95:5, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{15}H_{14}FN$ (227.28)

Calcd:	C, 74.70%;	H, 7.38%;	N, 5.12%
Found:	C, 74.98%;	H, 7.70%;	N, 5.18%

Data for (-)-**65b**:

m.p.: 88–90 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.27 – 7.21 (m, 4H, HC(13) and HC(14)), 7.17 – 7.11 (m, 1H, HC(15)), 6.72 – 6.65 (m, 2H, HC(10)), 6.39 – 6.29 (m, 2H (HC(9)), 4.22 (d, *J* = 6.6 Hz, 1H, HC(4)), 3.94 (qd, *J* = 6.5, 1.9 Hz, 1H, HC(2)), 1.87 (pd, *J* = 7.0, 1.9 Hz, 2H, HC(3)), 1.11 (d, *J* = 6.5 Hz, 3H, H_3C(1)), 0.90 (d, *J* = 7.1 Hz, 3H, H_3C(6)).

^{13}C NMR: (126 MHz, $CDCl_3$)

155.5 (d, *J* = 234.4 Hz, C(11)), 144.0 (d, *J* = 1.8 Hz, C(8)), 142.9 (C(12)), 128.5 (HC(14)), 126.97 (HC(15)), 126.96 (HC(13)), 115.4 (d, *J* = 22.2 Hz, HC(10)), 114.1 (d, *J* = 7.3 Hz, HC(9)), 68.4 (HC(2)), 62.9 (HC(4)), 44.6 (HC(3)), 21.1 (H_3C(1)), 12.26 (H_3C(6)).

^{19}F NMR: (471 MHz, $CDCl_3$)

-128.72 (tt, *J* = 8.1, 4.0 Hz).

IR: (neat)

3391 (w), 3028 (w), 2972 (w), 2934 (w), 1613 (w), 1509 (s), 1452 (w), 1404 (w), 1382 (w), 1354 (w), 1315 (w), 1264 (w), 1217 (m), 1155 (w), 1131 (w), 1097 (w), 1074 (w), 1029 (w), 995 (w), 913 (w), 897 (w), 861 (w), 818 (m), 773 (m), 737 (w), 702 (m), 637 (w), 509 (w).

LRMS: (EI, 70 eV)

75.0 (10), 91.1 (11), 95.0 (37), 111.0 (13), 115.1 (15), 117.1 (34), 118.1 (25), 122.0 (45), 137.1 (27), 198.1 (37), 199.1 (33), 200.1 (100), 201.1 (14), 255.1 (21).

TLC: R_f 0.62 (silica gel, hexanes/EtOAc, 1:1, UV)

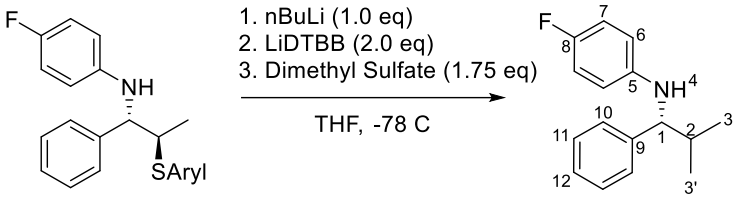
Opt. Rot.: $[\alpha]_D^{24}$ -8.6 (*c* = 1.30, 100% EtOH)

HPLC: t_R 36.7 min (99.6%); t_R 39.9 min (0.4%) (Supelco Astec, hexanes/*i*-PrOH, 98:2, 0.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{15}H_{14}FN$ (227.28)

Calcd:	C, 74.70%;	H, 7.38%;	N, 5.12%
Found:	C, 74.88%;	H, 7.68%;	N, 5.17%

Preparation of (*R*)-4-Fluoro-N-(2-methyl-1-phenylpropyl)aniline (66)



(1*S*, 2*R*)-**13** (*R*)-**66**

To an oven-dried, 25-mL Schlenk flask fitted with a Teflon stir bar, internal digital thermometer and a rubber septum was added (1*S*, 2*R*)- **13** (422 mg, 1.00 mmol) and dissolved in THF (10 mL). The solution was cooled to an internal temperature of 2 °C (ice/water bath). *n*-BuLi (430 μL, 2.3 M, 1.00 mmol, 1.0 equiv) was added dropwise via syringe over 5 min. During the course of the addition the internal temperature rose to 6 °C. The reaction was stirred at 0 °C for 20 min and subsequently cooled to an internal temperature of -74 °C (dry ice/*i*-PrOH) bath. Preformed LiDTBB (2.2 mL, 0.9M, 2.0 equiv, 2.0 mmol) was dropwise added to the reaction mixture over 10 min maintaining the internal temperature below -55 °C. During addition reaction became amber and upon complete addition the reaction was dark green. The mixture was stirred at -78 °C for an additional 2 min at which time dimethyl sulfate (166 ul, 1.75 equiv, 1.75 mmol) was added dropwise via syringe. The solution turned dark tan. The mixture was warmed to 23 °C and diluted with ether (10 mL), decanted into a 120-mL separatory funnel, and further diluted with ether (5 mL) and brine (10 mL). The organics were removed and the aqueous layer extracted with ether (2 x 15 mL). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (4 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) afford crude (-)-**66** as a white solid. Purification by column chromatography (38 g silica gel, 2 cm column, 10-mL fractions, isocratic hexanes/EtOAc, 24:1) afforded 218 mg (89%) of (-)-**66** as a white solid. Sublimation (55 °C, 0.2 mm Hg) afforded 201 mg (82%) of analytically pure (-)-**66** as a white solid.

Data for (-)-**66**:

m.p.: 69–70 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.25 – 7.17 (m, 4H, HC(10) and HC(11)), 7.17 – 7.12 (m, 1H, HC(12)), 6.74 – 6.64 (m, 2H, HC(7)), 6.34 (dd, *J* = 8.9, 4.3 Hz, 2H, HC(6)), 3.97 (d, *J* = 5.9 Hz, 1H, HC(1)), 3.92 (s, 1H, HN(4)), 2.01 – 1.88 (m, *J* = 6.5 Hz, 1H, HC(2)), 0.91 (d, *J* = 6.8 Hz, 3H, H_3C(3)), 0.84 (d, *J* = 6.8 Hz, 3H, H_3C(3')).

^{13}C NMR: (126 MHz, $CDCl_3$)

155.54 (d, *J* = 234.5 Hz, 1C, C(8)), 144.08 (C(5)), 142.35 (C(9)), 128.25 (HC(11)), 127.20 (HC(10)), 126.89 (HC(12)), 115.46 (d, *J* = 22.3 Hz, 1C, HC(7)), 113.97 (d, *J* = 7.2 Hz, 1C, HC(6)), 64.47 (HC(1)), 34.93 (HC(2)), 19.69 (H_3C(3')), 18.70 (H_3C(3)).

IR: (neat)

3431 (w), 3028 (w), 2961 (w), 2873 (w), 1613 (w), 1507 (s), 1467 (w), 1452 (w), 1400 (w), 1388 (w), 1368 (w), 1313 (w), 1266 (w), 1217 (m), 1177 (w), 1156 (w), 1141 (w), 1099 (w), 1064 (w), 1029 (w), 912 (w), 816 (s), 772 (m), 744 (m), 700 (s), 632 (w), 527 (m), 509 (m).

LRMS: (EI, 70 eV)

77.0 (12), 91.1 (12), 95.0 (19), 111.0 (14), 115.1 (13), 117.1 (12), 122.0 (20), 132.1 (11), 198.1 (14), 200.1 (100), 201.1 (15), 243.1 (19).

TLC: R_f 0.51 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

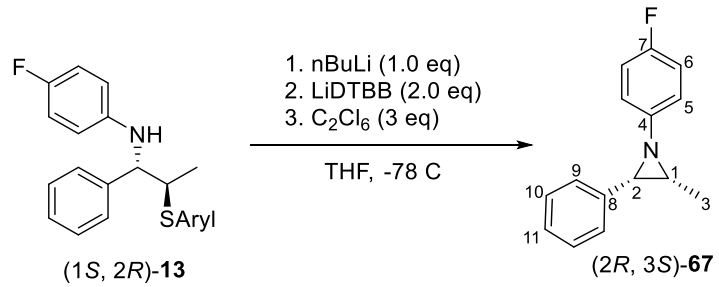
Opt. Rot.: $[\alpha]_D^{24}$ +33.2 (*c* = 1.01, 100% EtOH)

HPLC: t_R 9.19 min (98.9%); t_R 9.84 min (1.1%) (Supelco Astec, hexanes/*i*-PrOH, 95:5, 1.0 mL/min, 220 nm, 24 °C)

Analysis: $C_{15}H_{14}FN$ (227.28)

Calcd:	C, 79.27%;	H, 6.21%;	N, 6.16%
Found:	C, 78.94%;	H, 6.19%;	N, 5.97%

Preparation of (2*R*,3*S*)-1-(4-Fluorophenyl)-2-methyl-3-phenylaziridine (67)



To an oven-dried, 25-mL Schlenk flask fitted with a Teflon stir bar, internal digital thermometer and a rubber septum was added (1*S*, 2*R*)-**13** (422 mg, 1.00 mmol) and THF (10 mL). The solution was cooled to an internal temperature of 2 °C (ice/water bath). *n*-BuLi (1.0 equiv, 2.3 M, 430 μL, 1.00 mmol, 1.0 equiv) was added dropwise via syringe over 5 min. During the course of the addition the internal temperature rose to 6 °C. The reaction was stirred at 0 °C for 20 min and subsequently cooled to an internal temperature of -72 °C (dry ice/*i*-PrOH) bath. Preformed LiDTBB (2.2 mL, 0.9M, 2.0 equiv, 2.0 mmol) was dropwise added to the reaction mixture over 10 min maintaining the internal temperature below -65 °C. During addition reaction became amber and upon complete addition the reaction was dark green. The mixture was stirred at -78 °C for an additional 2 min at which time hexachloroethane (710 mg, 3 equiv, 3 mmol) dissolved in THF (1 mL) was added dropwise via syringe over approximately 15 seconds. The solution turned colorless. The reaction mixture was warmed to 23 °C, diluted with ether (5 mL), decanted into a 120-mL separatory funnel, and further diluted with ether (5 mL) and brine (10 mL). The organics were removed and the aqueous layer extracted with ether (3 x 25 ml). The combined organic layers were washed with 50% brine (20 mL), and then were dried over anhydrous Na_2SO_4 (6 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (-)-**67** as a white solid. Purification by column chromatography (66 g silica gel, 3 cm column, 10-mL fractions, hexanes/EtOAc gradient elution: 100:0 (100 mL) to 19:1 (500 mL)) afforded (-)-**67** as a clear, impure oil. (-)-**67** was chromatographed again (27 g silica gel, 2 cm column, hexanes/EtOAc gradient elution: 100:0 hexanes (100 mL) to 99:1 (100 mL) to 98:2 (100 mL) to 97:3 (100 mL) to 95:5 (250 mL)) to afford 192 mg (85%) of (-)-**67** as a clear oil. Further purification via Kugelrohr distillation (95 °C, 0.2 mm Hg) provided 183 mg (81%) of analytically pure (-)-**67** as clear oil.

Data for (-)-**67**:

b.p.: 95 °C (200 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.47 – 7.41 (m, 2H, HC(10)), 7.39 (t, *J* = 7.8 Hz, 2H, HC(9)), 7.36 – 7.29 (m, 1H, HC(11)), 7.03 – 6.98 (m, 2H, HC(5)), 6.96 (td, *J* = 9.0, 2.1 Hz, 2H, HC(6)), 3.28 (d, *J* = 6.6 Hz, 1H, HC(2)), 2.53 (p, *J* = 5.6 Hz, 1H, HC(1)), 1.16 (d, *J* = 5.9 Hz, 3H, H_3C(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

158.5 (d, *J* = 240.0 Hz, 1C, C(7)), 151.6 (d, *J* = 2.9 Hz, 1C, C(4)), 136.7 C(8)), 128.2 HC(10)), 127.7 HC(9)), 127.1 HC(11)), 121.0 (d, *J* = 8.0 Hz, 1C, HC(5)), 115.6 (d, *J* = 22.4 Hz, 1C, HC(6)), 46.8 HC(2)), 42.2 HC(1)), 13.4 H_3C(3)).

IR: (neat)

3029 (w), 2964 (w), 2927 (w), 1604 (w), 1502 (s), 1451 (m), 1414 (m), 1383 (w), 1356 (w), 1312 (w), 1271 (w), 1210 (s), 1180 (m), 1152 (w), 1144 (w), 1115 (w), 1094 (w), 1075 (w), 1044 (w), 1029 (w), 1016 (w), 992 (w), 903 (w), 835 (s), 817 (m), 780 (w), 756 (m), 712 (m), 699 (s), 624 (w), 562 (m), 525 (m), 497 (w), 474 (w).

LRMS: (EI, 70 eV)

95.0 (33), 136.1 (100), 200.1 (16), 212.1 (46), 224.1 (19), 225.1 (25), 226.1 (22), 227.1 (42).

TLC: R_f 0.60 (silica gel, hexanes/EtOAc, 9:1, UV/CAM)

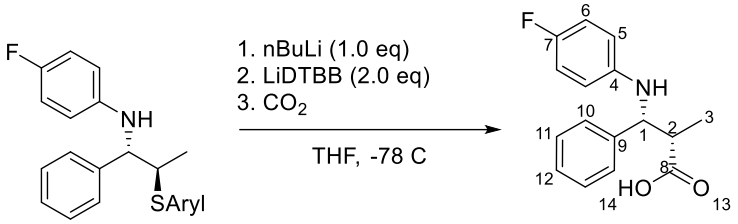
Opt. Rot.: $[\alpha]_D^{24}$ -239.6 (*c* = 1.37, 100% EtOH)

HPLC: t_R 9.7 min (98.9%); t_R 10.3 min (1.1%) (Supelco Astec, hexanes/*i*-PrOH, 97:3, 0.5 mL/min, 220 nm, 24 °C)

Analysis: $C_{15}H_{14}FN$ (227.28)

Calcd:	C, 79.27%;	H, 6.21%;	N, 6.16%
Found:	C, 78.94%;	H, 6.19%;	N, 5.97%

Preparation of (2*S*,3*R*)-3-((4-Fluorophenyl)amino)-2-methyl-3-phenylpropanoic Acid (68)



(1*S*, 2*R*)-**13** (2*S*, 3*R*)-**68**

To an oven-dried, 25-mL Schlenk flask fitted with a Teflon stir bar, internal digital thermometer and a rubber septum was added (1*S*, 2*R*)-**13** (422 mg, 1.00 mmol) and THF (10 mL). The solution was cooled to an internal temperature of 1 °C (ice/water bath). *n*-BuLi (430 μL, 2.3 M, 1.00 mmol, 1.0 equiv) was added dropwise via syringe over 10 min. During the course of the addition the internal temperature rose to 4 °C. The reaction was stirred at 0 °C for 20 min and subsequently cooled to an internal temperature of -72 °C (dry ice/*i*-PrOH) bath. Preformed LiDTBB (2.2 mL, 0.9M, 2.0 equiv, 2.0 mmol) was dropwise added to the reaction mixture over 10 min maintaining the internal temperature below -65 °C. During addition the reaction mixture became amber and upon complete addition the reaction was dark green. The mixture was stirred at -78 °C for an additional 2 min at which time gaseous carbon dioxide was bubbled in via a balloon equipped with a syringe and needle extending into the reaction mixture. The solution turned colorless within a few seconds. The reaction was warmed to 23 °C, diluted with ether (5 mL), and decanted into a 100-mL round bottomed flask and concentrated under reduced pressure (15 mm Hg, 23 °C). The residual solids were taken up in pentane and sonicated at 23 °C and cooled to -20 °C for 30 min. Vacuum filtration of this suspension yielded the crude, hydroscopic carbamate which was washed with cold pentane (20 mL). The solid was transferred to a 50-mL Erlenmeyer flask and suspended in ether (10 mL) and water (4 mL) was added. The pH of the aqueous phase was carefully adjusted to pH of 3 by dropwise addition of 1M HCl and 1M NaOH. The biphasic mixture was decanted to a 60-mL separatory funnel, the organics removed and the aqueous layer extracted with ether (4 x 10 mL). The combined organic layers were dried with sodium sulfate (4 g), filtered, and concentrated under reduced pressure (15 mm Hg, 30 °C). Purification by column chromatography (25 g silica gel, 2 cm column, 10-ml fractions, isocratic CH_2Cl_2/MeOH, 24:1) afforded 195 mg (72%) of (-)-**68** as a tan solid. The product was purified by trituration as follows. The crude material was suspended in pentane (2

mL) and sonicated at 23 °C and cooled to -20 °C for 12 h. Vacuum filtration of this suspension yielded 187 mg (69%) of analytically pure (-)-**68** as a fine, tan powder.

Data for (-)-**68**:

m.p.: 118–120 °C (pentane)

^{1}H NMR: (500 MHz, D_3COD)

7.37 (dd, *J* = 8.1, 1.5 Hz, 2H, HC(10)), 7.30 (t, *J* = 7.6 Hz, 2H, HC(11)), 7.26 – 7.14 (m, 1H, HC(12)), 6.81 – 6.69 (m, 2H, HC(6)), 6.62 – 6.50 (m, 2H, HC(5)), 4.50 (d, *J* = 8.9 Hz, 1H, HC(1)), 2.81 (dq, *J* = 9.0, 7.0 Hz, 1H, HC(2)), 1.02 (d, *J* = 7.0 Hz, 3H, H_3C(3)).

^{13}C NMR: (126 MHz, D_3COD)

177.7 (C(8)), 155.5 (d, *J* = 233.2 Hz, C(7)), 144.0 (d, *J* = 1.9 Hz, C(4)), 141.2 (C(9)), 128.0 (HC(11)), 127.2 (HC(10)), 126.9 (HC(12)), 114.6 (d, *J* = 19.4 Hz, HC(6)), 114.4 (d, *J* = 4.3 Hz, HC(5)), 61.0 (HC(1)), 46.4 (HC(2)), 14.1 (H_3C(3)).

IR: (neat)

3311 (w), 2986 (w), 1680 (m), 1507 (s), 1456 (m), 1411 (w), 1385 (w), 1354 (w), 1299 (m), 1244 (m), 1220 (s), 1204 (s), 1156 (m), 1109 (m), 1093 (m), 1059 (m), 1030 (m), 884 (m), 855 (m), 830 (s), 787 (m), 771 (m), 745 (s), 735 (s), 701 (s), 662 (m), 635 (m), 566 (m), 542 (s), 520 (m), 496 (m), 486 (m).

LRMS: (EI, 70 eV)

55.1 (12), 57.1 (17), 77.0 (14), 83.0 (11), 91.1 (38), 95.0 (36), 111.0 (25), 115.1 (15), 117.1 (32), 118.1 (27), 122.0 (37), 198.1 (21), 199.1 (10), 200.1 (49), 229.1 (15), 251.2 (100), 252.2 (21), 266.2 (31).

TLC: R_f 0.60 (silica gel, CH_2Cl_2/MeOH, 9:1, UV)

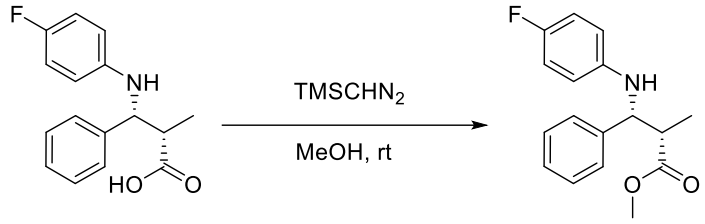
Opt. Rot.: $[\alpha]_D^{24}$ +23.1 (*c* = 1.11, 100% EtOH)

SFC: t_R 12.3 min (0.7%); t_R 13.4 min (99.3%) (Chiralpak OD, CO_2/MeOH, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 (10 min); isocratic 10% MeOH/CO_2 (10 min), 2.5 mL/min, 220 nm, 24 °C) [determined with derivative **68a**]

Analysis: $C_{16}H_{16}FNO_2$ (273.30)

Calcd:	C, 70.31%;	H, 5.90%;	N, 5.12%
Found:	C, 70.67%;	H, 6.30%;	N, 5.18%

Preparation of Methyl (2*S*,3*R*)-3-((4-fluorophenyl)amino)-2-methyl-3-phenylpropanoate (68a)



(2*S*, 3*R*)-**68** (2*S*, 3*R*)-**68a**

An oven-dried, 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (2*S*,3*R*)-**68** (10 mg, 0.036 mmol) and MeOH (0.50 mL). (Trimethylsilyl)diazomethane (2M in hexanes, 36 µl, 0.073 mmol, 2.0 equiv) was added in a single portion. Full conversion was observed by TLC (hexanes/EtOAc, 5:1). The reaction mixture was decanted into a 10-mL round-bottomed flask and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **68a**. The product was chromatographed (6 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 9 mg (85%) of **68a** as a clear oil.

Data for **68a**:

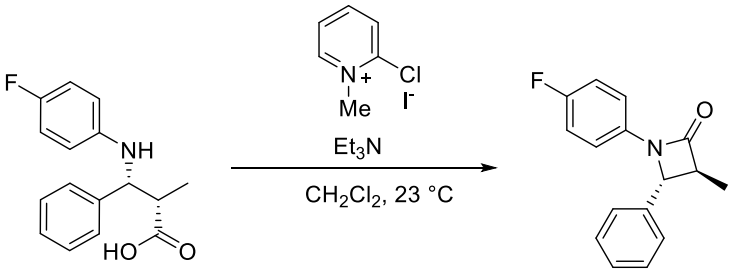
^{1}H NMR: (500 MHz, $CDCl_3$)

7.36 – 7.31 (m, 2H), 7.32 – 7.22 (m, 3H), 6.80 (t, J = 8.7 Hz, 2H), 6.49 (dd, J = 9.0, 4.4 Hz, 2H), 4.45 (d, J = 7.6 Hz, 1H), 3.66 (s, 3H), 2.87 (p, J = 7.2 Hz, 1H), 1.18 (d, J = 7.0 Hz, 3H).

HRMS: (EI, 70 eV)

Calcd for $C_{17}H_{18}NO_2S$ ($[M]^+$): 287.1322, Found: 287.1329

Preparation of (3*S*,4*R*)-1-(4-Fluorophenyl)-3-methyl-4-phenylazetidin-2-one (69)



(2*S*, 3*R*)-**68** (3*S*,4*R*)-**69**

To an oven-dried, 100-mL Schlenk flask fitted with a Teflon stir bar and a rubber septum was added (1*S*, 2*R*)- **68** (273 mg, 1.0 mmol) and CH_2Cl_2 (50 mL) to give a clear, homogeneous, solution. Freshly distilled Et_3N (0.28 mL, 2.0 mmol, 2.0 equiv) was added in a single portion at 23 °C followed by the addition of 2-Chloro-1-methylpyridinium iodide (281 mg, 1.1 equiv, 1.10 mmol) in a single portion. The solution became yellow. The reaction was stirred at 23 °C for 4 h. Full conversion was confirmed by TLC (CH_2Cl_2/MeOH, 4:1). The solution was decanted into a 250-mL, round bottomed flask and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford a yellow solid. Purification by column chromatography (30 g silica gel, 2 cm column, 10-mL fractions, isocratic hexanes/EtOAc, 95:5) afforded 127 mg (50%) of **69** as a clear oil that solidified to a white solid on standing. Spectroscopic data matched those previously reported.[133]

Data for **69**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.42 – 7.31 (m, 5H), 7.28 – 7.21 (m, 2H), 6.98 – 6.88 (m, 2H), 4.56 (d, *J* = 2.4 Hz, 1H), 3.15 (qd, *J* = 7.4, 2.4 Hz, 1H), 1.49 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$)

168.2, 160.0, 158.1, 137.8, 134.2 (d, *J* = 2.7 Hz), 129.3, 128.7, 126.0, 118.5 (d, *J* = 7.8 Hz), 115.9 (d, *J* = 22.7 Hz), 63.1, 55.7, 13.2.

^{19}F NMR: (471 MHz, $CDCl_3$)

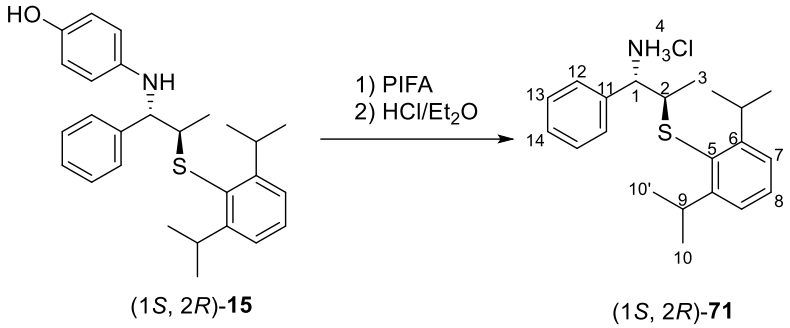
-118.28 (tt, *J* = 8.6, 4.8 Hz).

SFC: t_R5.4 min (0.5%); t_R 6.6 min (99.5%) (Chiralpak AD, CO_2/MeOH, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 (10 min); isocratic 10% MeOH/CO_2 (10 min), 2.5 mL/min, 220 nm, 24 °C)

HRMS: (EI, 70 eV)

Calcd for $C_{16}H_{14}ONF$ ($[M]^+$): 255.1059, Found: 255.1060

Preparation of Chloro((1*S*,2*R*)-2-((2,6-diisopropylphenyl)thio)-1-phenylpropyl)-l5-azane (71)



A 10-mL, round-bottomed flask with Teflon stir bar and rubber septum was charged with (1*S*, 2*R*)- **15** (420 mg, 1.00 mmol), MeCN (3 mL), water (2 mL) and cooled in an ice/water bath. [Bis(trifluoroacetoxy)iodo]benzene (559 mg, 1.30 mmol, 1.30 equiv) dissolved in MeCN (1 mL) was added dropwise to the reaction mixture over 3 min. A homogeneous, red solution resulted. The mixture was slowly warmed to 23 °C and stirred for 4 h. Full conversion was observed by TLC (hexanes/EtOAc, 4:1). The reaction mixture was concentrated under reduced pressure (40 °C, 15 mm Hg) to afford crude (+)-**71** as a brown solid. The solid was dissolved in EtOAc (10 mL) and decanted into a 60-mL separatory funnel. Potassium hydroxide (1M, 3 mL) was added resulting in the formation of a precipitate. The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude (+)-**71** as a brown oil. HCl in Et_2O (1M, 1.0 mL, 1.0 equiv) was added in a single portion resulting in the formation of a light brown precipitate. The suspension was sonicated at 23 °C and cooled to -20 °C for 1 h. Vacuum filtration of this suspension yielded a light brown powder which was washed with ether (10 mL) to afford 302 mg (83%) of analytically pure (+)-**71** as a fine, light brown powder.

Data for (+)-**71**:

m.p.: 197 °C (decomposition)

^{1}H NMR: (500 MHz, DMSO-d_6)

8.91 (br s, 3H, HN(4)), 7.65 – 7.62 (m, 2H, HC(12)), 7.51 – 7.39 (m, 3H, HC(13) and HC(14)), 7.33 (t, J = 7.7 Hz, 1H, HC(8)), 7.18 (d, J = 7.7 Hz, 2H, HC(7)), 4.24 (d, J = 9.5 Hz, 1H, HC(1)), 3.49 (br s, 2H, HC(9)), 3.41-3.33 (m, 1H, HC(2)), 1.22 (d, J = 6.6 Hz, 3H, H_3C(3)), 1.08 (d, J = 6.8 Hz, 6H, H_3C(10')), 1.03 (d, J = 6.8 Hz, 6H, H_3C(10)).

^{13}C NMR: (126 MHz, DMSO-d_6)

153.8 (C(6)), 137.4 (C(11)), 130.2 (HC(8)), 129.3 (HC(14)), 128.8 (C(5)), 128.8 (HC(13)), 128.4 (HC(12)), 124.2 (HC(7)), 58.8 (HC(1)), 49.3 (HC(2)), 31.3 (HC(9)), 25.0 (H_3C(10')), 24.1 (H_3C(10)), 18.3 (H_3C(3)).

IR: (neat)

3055 (w), 2958 (m), 2863 (w), 1593 (w), 1515 (s), 1457 (m), 1421 (w), 1380 (w), 1360 (w), 1312 (w), 1246 (w), 1221 (w), 1179 (w), 1145 (w), 1055 (w), 1033 (w), 1005 (w), 932 (w), 867 (w), 799 (w), 756 (m), 746 (m), 697 (s), 625 (w), 545 (m), 524 (w), 457 (w).

LRMS: (EI, 70 eV)

103.1 (13), 104.1 (15), 105.1 (18), 106.0 (100), 107.1 (14), 115.1 (74), 116.1 (20), 117.1 (65), 118.1 (26), 123.0 (13), 128.1 (21), 129.1 (14), 134.0 (32), 135.0 (30), 137.0 (23), 147.0 (21), 149.0 (96), 150.0 (14), 151.1 (27), 175.1 (33), 177.1 (54), 179.1 (34), 189.1 (13), 190.1 (19), 191.1 (43), 192.1 (21), 194.1 (21), 204.1 (28), 219.1 (88), 220.1 (12), 221.1 (17), 222.1 (36), 310.2 (25).

TLC: R_f 0.63 (silica gel, CH_2Cl_2/MeOH, 50:1, UV)

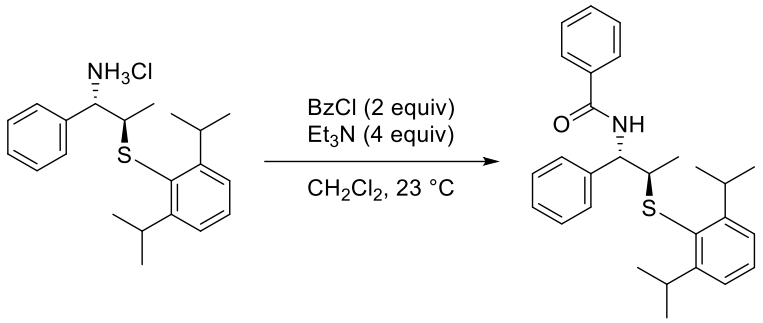
Opt. Rot.: $[\alpha]_D^{24}$ +10.5 (c = 1.13, 100% EtOH)

SFC: t_R 11.0 min (0.5%); t_R 13.4 min (99.5%) (Chiralpak OD, CO_2/MeOH, gradient 1% MeOH/CO_2 to 10% MeOH/CO_2 (10 min); isocratic 10% MeOH/CO_2 (10 min), 2.5 mL/min, 220 nm, 24 °C) [determined with derivative **71a**]

Analysis: $C_{21}H_{30}ClNS \cdot 0.15$ HCl (363.98)

Calcd:	C, 68.27%;	H, 8.23%;	N, 3.79%
Found:	C, 68.00%;	H, 8.47%;	N, 4.03%

Preparation of *N*-((1*S*,2*R*)-2-((2,6-diisopropylphenyl)thio)-1-phenylpropyl)benzamide (71a)



(1*S*, 2*R*)-**71** (1*S*, 2*R*)-**71a**

A 1-dram vial equipped with a Teflon stir bar and Teflon cap was charged with (1*S*, 2*R*)-**71** (10.0 mg, 0.027 mmol, 1.0 equiv), CH_2Cl_2 (300 μL), Et_3N (15 μL, 0.10 mmol, 4.0 equiv) and benzoyl chloride (7 μl, 0.055 mmol, 2 equiv) and the mixture was stirred at 23 °C for 2 h. Full conversion was observed by TLC (hexanes/EtOAc, 4:1). The reaction mixture was diluted with EtOAc (2 mL), decanted into a 10-mL separatory funnel. The flask was rinsed with EtOAc (2 x 2 mL) and the reaction mixture further diluted with brine (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure (30 °C, 15 mm Hg) to afford crude **71a**. The product was purified by chromatography (6 g silica gel, 1 cm column, dry load on Celite, 5-mL fractions, isocratic hexanes/EtOAc, 9:1) to afford 8 mg (67%) of **71a** as a white solid.

Data for **71a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.90 – 7.85 (m, 2H), 7.59 – 7.55 (m, 1H), 7.53 – 7.48 (m, 2H), 7.39 (d, J = 4.3 Hz, 4H), 7.37 – 7.30 (m, 2H), 7.18 (d, J = 7.7 Hz, 2H), 7.10 – 7.04 (m, 1H), 5.36 – 5.28 (m, 1H), 3.87 (hept, J = 6.9 Hz, 2H), 3.38 (qd, J = 6.9, 4.7 Hz, 1H), 1.20 (dd, J = 6.9, 4.6 Hz, 9H), 1.16 (d, J = 6.8 Hz, 6H).

HRMS: (EI, 70 eV)

Calcd for $C_{28}H_{33}NOS$ ($[M]^+$): 431.2283, Found: 431.2299

Crystal structure data for *N*-((1*S*,2*R*)-2-((2,6-Diisopropylphenyl)thio)-1-phenylpropyl)-4-fluoroaniline (13)

Table 12. Crystal data and structure refinement for dd75usa.

Identification code	dd75usa	
Empirical formula	C27 H32 F N S	
Formula weight	421.59	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$C222_1$	
Unit cell dimensions	a = 9.9111(2) Å	α= 90°.
	b = 19.1719(4) Å	β= 90°.
	c = 24.7720(5) Å	γ = 90°.
Volume	4707.04(17) $Å^3$	
Z	8	
Density (calculated)	1.190 Mg/m^3	
Absorption coefficient	1.375 mm^{-1}	
F(000)	1808	
Crystal size	0.548 x 0.300 x 0.148 mm^3	
Theta range for data collection	3.568 to 68.246°.	
Index ranges	-11<=h<=11, -23<=k<=23, -29<=l<=29	
Reflections collected	49018	
Independent reflections	4304 [R(int) = 0.0237]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Integration	
Max. and min. transmission	1.0000 and 0.6467	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4304 / 223 / 313	
Goodness-of-fit on F^2	1.075	
Final R indices [I>2sigma(I)]	R1 = 0.0232, wR2 = 0.0620	
R indices (all data)	R1 = 0.0232, wR2 = 0.0621	
Absolute structure parameter	0.000(2)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.161 and -0.205 e.$Å^{-3}$	

Table 13. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for dd75usa. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3819(1)	2897(1)	4541(1)	19(1)
N(1)	4955(2)	4307(1)	4015(1)	21(1)
C(1)	2453(2)	2703(1)	4091(1)	18(1)
C(2)	1409(2)	3196(1)	4020(1)	20(1)
C(3)	323(2)	3018(1)	3690(1)	24(1)
C(4)	259(2)	2379(1)	3434(1)	25(1)
C(5)	1274(2)	1896(1)	3512(1)	23(1)
C(6)	2382(2)	2042(1)	3840(1)	19(1)
C(7)	1402(2)	3900(1)	4305(1)	23(1)
C(8)	665(3)	3834(1)	4844(1)	41(1)
C(9)	776(2)	4485(1)	3968(1)	29(1)
C(10)	3424(2)	1467(1)	3924(1)	21(1)
C(11)	4008(2)	1209(1)	3388(1)	29(1)
C(12)	2798(2)	861(1)	4241(1)	26(1)
C(13)	5250(2)	3034(1)	4080(1)	19(1)
C(14)	6513(2)	3092(1)	4430(1)	33(1)
C(15)	5044(2)	3664(1)	3702(1)	17(1)
C(16)	6179(2)	3693(1)	3288(1)	18(1)
C(17)	6309(2)	3152(1)	2914(1)	21(1)
C(18)	7322(2)	3164(1)	2528(1)	25(1)
C(19)	8218(2)	3721(1)	2506(1)	27(1)
C(20)	8106(2)	4257(1)	2877(1)	27(1)
C(21)	7094(2)	4242(1)	3267(1)	22(1)
F(1)	2244(4)	6663(2)	3383(3)	47(1)
C(22)	4325(9)	4899(3)	3835(3)	24(1)
C(23)	3934(8)	4996(3)	3301(3)	27(1)
C(24)	3239(6)	5595(3)	3153(2)	28(1)
C(25)	2935(4)	6099(2)	3538(3)	28(1)
C(26)	3326(5)	6002(3)	4072(3)	31(1)
C(27)	4022(7)	5402(3)	4220(2)	28(1)
F(1A)	2308(5)	6593(3)	3101(4)	46(1)

Table 13 (cont.)

C(22A)	4229(11)	4891(4)	3776(3)	24(1)
C(23A)	4015(10)	4911(4)	3222(3)	24(1)
C(24A)	3376(7)	5482(4)	2990(3)	30(1)
C(25A)	2951(5)	6034(3)	3312(3)	31(1)
C(26A)	3165(6)	6014(3)	3866(3)	28(1)
C(27A)	3803(9)	5442(4)	4098(3)	27(1)

Table 14. Bond lengths [Å] and angles [°] for dd75usa.

S(1)-C(1)	1.7924(17)
S(1)-C(13)	1.8388(17)
N(1)-C(22)	1.371(4)
N(1)-C(22A)	1.457(4)
N(1)-C(15)	1.458(2)
N(1)-H(1)	0.84(2)
C(1)-C(2)	1.413(2)
C(1)-C(6)	1.414(2)
C(2)-C(3)	1.394(2)
C(2)-C(7)	1.522(2)
C(3)-C(4)	1.381(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.381(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.394(2)
C(5)-H(5)	0.9500
C(6)-C(10)	1.525(2)
C(7)-C(8)	1.528(3)
C(7)-C(9)	1.529(3)
C(7)-H(7)	1.0000
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800

Table 14 (cont.)

C(9)-H(9C)	0.9800
C(10)-C(11)	1.529(2)
C(10)-C(12)	1.533(2)
C(10)-H(10)	1.0000
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(14)	1.527(2)
C(13)-C(15)	1.542(2)
C(13)-H(13)	1.0000
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-C(16)	1.524(2)
C(15)-H(15)	1.0000
C(16)-C(21)	1.389(2)
C(16)-C(17)	1.398(2)
C(17)-C(18)	1.386(3)
C(17)-H(17)	0.9500
C(18)-C(19)	1.390(3)
C(18)-H(18)	0.9500
C(19)-C(20)	1.383(3)
C(19)-H(19)	0.9500
C(20)-C(21)	1.392(3)
C(20)-H(20)	0.9500
C(21)-H(21)	0.9500
F(1)-C(25)	1.337(5)
C(22)-C(23)	1.3900
C(22)-C(27)	1.3900
C(23)-C(24)	1.3900
C(23)-H(23)	0.9500
C(24)-C(25)	1.3900

Table 14 (cont.)

C(24)-H(24)	0.9500
C(25)-C(26)	1.3900
C(26)-C(27)	1.3900
C(26)-H(26)	0.9500
C(27)-H(27)	0.9500
F(1A)-C(25A)	1.353(6)
C(22A)-C(23A)	1.3900
C(22A)-C(27A)	1.3900
C(23A)-C(24A)	1.3900
C(23A)-H(23A)	0.9500
C(24A)-C(25A)	1.3900
C(24A)-H(24A)	0.9500
C(25A)-C(26A)	1.3900
C(26A)-C(27A)	1.3900
C(26A)-H(26A)	0.9500
C(27A)-H(27A)	0.9500
C(1)-S(1)-C(13)	103.10(7)
C(22)-N(1)-C(15)	123.7(4)
C(22A)-N(1)-C(15)	117.6(4)
C(22)-N(1)-H(1)	109.9(16)
C(22A)-N(1)-H(1)	113.7(17)
C(15)-N(1)-H(1)	114.0(16)
C(2)-C(1)-C(6)	120.63(15)
C(2)-C(1)-S(1)	119.43(13)
C(6)-C(1)-S(1)	119.80(12)
C(3)-C(2)-C(1)	118.31(15)
C(3)-C(2)-C(7)	119.02(15)
C(1)-C(2)-C(7)	122.62(15)
C(4)-C(3)-C(2)	121.47(16)
C(4)-C(3)-H(3)	119.3
C(2)-C(3)-H(3)	119.3
C(5)-C(4)-C(3)	119.81(16)
C(5)-C(4)-H(4)	120.1
C(3)-C(4)-H(4)	120.1
C(4)-C(5)-C(6)	121.41(16)

Table 14 (cont.)

C(4)-C(5)-H(5)	119.3
C(6)-C(5)-H(5)	119.3
C(5)-C(6)-C(1)	118.35(15)
C(5)-C(6)-C(10)	117.96(15)
C(1)-C(6)-C(10)	123.65(15)
C(2)-C(7)-C(8)	109.55(14)
C(2)-C(7)-C(9)	113.49(15)
C(8)-C(7)-C(9)	110.11(16)
C(2)-C(7)-H(7)	107.8
C(8)-C(7)-H(7)	107.8
C(9)-C(7)-H(7)	107.8
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(6)-C(10)-C(11)	111.81(14)
C(6)-C(10)-C(12)	110.04(15)
C(11)-C(10)-C(12)	110.62(14)
C(6)-C(10)-H(10)	108.1
C(11)-C(10)-H(10)	108.1
C(12)-C(10)-H(10)	108.1
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5

Table 14 (cont.)

C(10)-C(12)-H(12A)	109.5
C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(14)-C(13)-C(15)	113.33(14)
C(14)-C(13)-S(1)	106.93(12)
C(15)-C(13)-S(1)	112.70(11)
C(14)-C(13)-H(13)	107.9
C(15)-C(13)-H(13)	107.9
S(1)-C(13)-H(13)	107.9
C(13)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(13)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
N(1)-C(15)-C(16)	111.77(13)
N(1)-C(15)-C(13)	110.35(13)
C(16)-C(15)-C(13)	109.86(13)
N(1)-C(15)-H(15)	108.3
C(16)-C(15)-H(15)	108.3
C(13)-C(15)-H(15)	108.3
C(21)-C(16)-C(17)	118.48(15)
C(21)-C(16)-C(15)	122.37(14)
C(17)-C(16)-C(15)	119.15(15)
C(18)-C(17)-C(16)	120.81(16)
C(18)-C(17)-H(17)	119.6
C(16)-C(17)-H(17)	119.6
C(17)-C(18)-C(19)	120.13(16)
C(17)-C(18)-H(18)	119.9
C(19)-C(18)-H(18)	119.9
C(20)-C(19)-C(18)	119.55(17)
C(20)-C(19)-H(19)	120.2

Table 14 (cont.)

C(18)-C(19)-H(19)	120.2
C(19)-C(20)-C(21)	120.24(17)
C(19)-C(20)-H(20)	119.9
C(21)-C(20)-H(20)	119.9
C(16)-C(21)-C(20)	120.78(16)
C(16)-C(21)-H(21)	119.6
C(20)-C(21)-H(21)	119.6
N(1)-C(22)-C(23)	123.2(5)
N(1)-C(22)-C(27)	116.7(5)
C(23)-C(22)-C(27)	120.0
C(24)-C(23)-C(22)	120.0
C(24)-C(23)-H(23)	120.0
C(22)-C(23)-H(23)	120.0
C(23)-C(24)-C(25)	120.0
C(23)-C(24)-H(24)	120.0
C(25)-C(24)-H(24)	120.0
F(1)-C(25)-C(24)	118.4(3)
F(1)-C(25)-C(26)	121.6(3)
C(24)-C(25)-C(26)	120.0
C(27)-C(26)-C(25)	120.0
C(27)-C(26)-H(26)	120.0
C(25)-C(26)-H(26)	120.0
C(26)-C(27)-C(22)	120.0
C(26)-C(27)-H(27)	120.0
C(22)-C(27)-H(27)	120.0
C(23A)-C(22A)-C(27A)	120.0
C(23A)-C(22A)-N(1)	119.8(5)
C(27A)-C(22A)-N(1)	120.1(5)
C(22A)-C(23A)-C(24A)	120.0
C(22A)-C(23A)-H(23A)	120.0
C(24A)-C(23A)-H(23A)	120.0
C(25A)-C(24A)-C(23A)	120.0
C(25A)-C(24A)-H(24A)	120.0
C(23A)-C(24A)-H(24A)	120.0
F(1A)-C(25A)-C(24A)	121.6(4)

Table 14 (cont.)

F(1A)-C(25A)-C(26A)	118.4(4)
C(24A)-C(25A)-C(26A)	120.0
C(27A)-C(26A)-C(25A)	120.0
C(27A)-C(26A)-H(26A)	120.0
C(25A)-C(26A)-H(26A)	120.0
C(26A)-C(27A)-C(22A)	120.0
C(26A)-C(27A)-H(27A)	120.0
C(22A)-C(27A)-H(27A)	120.0

Symmetry transformations used to generate equivalent atoms:

Table 15. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for dd75usa. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	23(1)	16(1)	18(1)	0(1)	-2(1)	-1(1)
N(1)	29(1)	15(1)	20(1)	-1(1)	4(1)	0(1)
C(1)	17(1)	17(1)	19(1)	3(1)	2(1)	-1(1)
C(2)	20(1)	15(1)	24(1)	4(1)	6(1)	0(1)
C(3)	15(1)	19(1)	36(1)	7(1)	2(1)	1(1)
C(4)	19(1)	22(1)	35(1)	6(1)	-6(1)	-4(1)
C(5)	23(1)	16(1)	30(1)	0(1)	-2(1)	-3(1)
C(6)	19(1)	14(1)	23(1)	2(1)	2(1)	-1(1)
C(7)	23(1)	16(1)	29(1)	0(1)	7(1)	2(1)
C(8)	61(1)	26(1)	37(1)	-3(1)	24(1)	0(1)
C(9)	27(1)	18(1)	43(1)	1(1)	3(1)	4(1)
C(10)	22(1)	14(1)	28(1)	-2(1)	-4(1)	2(1)
C(11)	25(1)	28(1)	34(1)	-2(1)	3(1)	4(1)
C(12)	30(1)	16(1)	30(1)	1(1)	-2(1)	3(1)
C(13)	18(1)	16(1)	23(1)	1(1)	-2(1)	0(1)
C(14)	27(1)	33(1)	39(1)	13(1)	-14(1)	-6(1)
C(15)	17(1)	15(1)	20(1)	0(1)	-2(1)	1(1)
C(16)	16(1)	18(1)	20(1)	1(1)	-4(1)	3(1)
C(17)	20(1)	19(1)	23(1)	-1(1)	-4(1)	1(1)
C(18)	24(1)	27(1)	23(1)	-6(1)	-2(1)	3(1)
C(19)	19(1)	33(1)	28(1)	-1(1)	2(1)	3(1)
C(20)	18(1)	27(1)	36(1)	-2(1)	0(1)	-3(1)
C(21)	19(1)	20(1)	28(1)	-4(1)	-1(1)	2(1)
F(1)	29(1)	19(1)	92(3)	10(2)	-4(2)	5(1)
C(22)	17(1)	15(1)	39(2)	3(1)	7(1)	-2(1)
C(23)	20(2)	16(2)	46(2)	2(2)	3(2)	3(2)
C(24)	19(2)	18(2)	47(3)	5(2)	-2(2)	2(2)
C(25)	17(2)	12(2)	55(3)	9(2)	2(2)	4(1)
C(26)	23(2)	18(2)	53(3)	-1(2)	8(2)	-1(2)
C(27)	21(2)	17(2)	46(2)	0(2)	8(2)	0(2)
F(1A)	28(2)	20(2)	90(4)	20(2)	-8(3)	5(1)

Table 15 (cont.)

C(22A)	17(1)	15(1)	39(2)	3(1)	7(1)	-2(1)
C(23A)	16(2)	16(2)	40(2)	9(2)	1(2)	2(2)
C(24A)	21(2)	20(2)	49(3)	6(2)	0(2)	2(2)
C(25A)	22(2)	17(2)	55(3)	4(2)	2(2)	0(2)
C(26A)	20(2)	10(2)	54(3)	10(2)	6(2)	7(2)
C(27A)	22(3)	15(2)	44(3)	7(2)	8(2)	1(2)

Table 16. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{3}) for dd75usa.

	x	y	z	U(eq)
H(1)	4780(20)	4244(12)	4344(10)	32
H(3)	-390	3343	3641	28
H(4)	-481	2272	3205	30
H(5)	1216	1455	3339	28
H(7)	2359	4030	4383	27
H(8A)	-263	3678	4781	62
H(8B)	654	4288	5026	62
H(8C)	1132	3493	5072	62
H(9A)	1185	4488	3608	44
H(9B)	939	4934	4146	44
H(9C)	-198	4407	3936	44
H(10)	4181	1663	4144	26
H(11A)	3291	991	3174	43
H(11B)	4719	866	3460	43
H(11C)	4387	1604	3189	43
H(12A)	2024	676	4041	38
H(12B)	2497	1029	4595	38
H(12C)	3471	493	4289	38
H(13)	5343	2607	3851	23
H(14A)	7310	3131	4198	49
H(14B)	6595	2675	4657	49

Table 16 (cont.)

H(14C)	6446	3506	4660	49
H(15)	4173	3599	3505	21
H(17)	5696	2771	2924	25
H(18)	7404	2790	2278	30
H(19)	8903	3734	2238	32
H(20)	8721	4636	2866	32
H(21)	7028	4611	3522	26
H(23)	4142	4652	3038	33
H(24)	2971	5662	2788	34
H(26)	3119	6346	4335	38
H(27)	4289	5336	4585	33
H(23A)	4306	4534	3002	29
H(24A)	3230	5496	2611	36
H(26A)	2874	6391	4086	34
H(27A)	3949	5428	4477	33

Table 17. Torsion angles [°] for dd75usa.

C(13)-S(1)-C(1)-C(2)	-109.33(13)
C(13)-S(1)-C(1)-C(6)	75.00(14)
C(6)-C(1)-C(2)-C(3)	-1.0(2)
S(1)-C(1)-C(2)-C(3)	-176.60(12)
C(6)-C(1)-C(2)-C(7)	176.62(15)
S(1)-C(1)-C(2)-C(7)	1.0(2)
C(1)-C(2)-C(3)-C(4)	-0.5(2)
C(7)-C(2)-C(3)-C(4)	-178.16(16)
C(2)-C(3)-C(4)-C(5)	1.4(3)
C(3)-C(4)-C(5)-C(6)	-0.9(3)
C(4)-C(5)-C(6)-C(1)	-0.5(3)
C(4)-C(5)-C(6)-C(10)	177.30(16)
C(2)-C(1)-C(6)-C(5)	1.4(2)
S(1)-C(1)-C(6)-C(5)	177.05(13)
C(2)-C(1)-C(6)-C(10)	-176.20(15)
S(1)-C(1)-C(6)-C(10)	-0.6(2)

Table 17 (cont.)

C(3)-C(2)-C(7)-C(8)	87.2(2)
C(1)-C(2)-C(7)-C(8)	-90.4(2)
C(3)-C(2)-C(7)-C(9)	-36.3(2)
C(1)-C(2)-C(7)-C(9)	146.12(16)
C(5)-C(6)-C(10)-C(11)	57.0(2)
C(1)-C(6)-C(10)-C(11)	-125.32(17)
C(5)-C(6)-C(10)-C(12)	-66.3(2)
C(1)-C(6)-C(10)-C(12)	111.33(18)
C(1)-S(1)-C(13)-C(14)	-171.44(12)
C(1)-S(1)-C(13)-C(15)	63.38(13)
C(22)-N(1)-C(15)-C(16)	81.1(5)
C(22A)-N(1)-C(15)-C(16)	82.4(5)
C(22)-N(1)-C(15)-C(13)	-156.4(5)
C(22A)-N(1)-C(15)-C(13)	-155.0(5)
C(14)-C(13)-C(15)-N(1)	-58.39(19)
S(1)-C(13)-C(15)-N(1)	63.22(16)
C(14)-C(13)-C(15)-C(16)	65.29(18)
S(1)-C(13)-C(15)-C(16)	-173.09(11)
N(1)-C(15)-C(16)-C(21)	6.9(2)
C(13)-C(15)-C(16)-C(21)	-115.94(17)
N(1)-C(15)-C(16)-C(17)	-172.91(14)
C(13)-C(15)-C(16)-C(17)	64.24(18)
C(21)-C(16)-C(17)-C(18)	-0.4(2)
C(15)-C(16)-C(17)-C(18)	179.41(15)
C(16)-C(17)-C(18)-C(19)	-0.6(3)
C(17)-C(18)-C(19)-C(20)	1.1(3)
C(18)-C(19)-C(20)-C(21)	-0.6(3)
C(17)-C(16)-C(21)-C(20)	0.9(2)
C(15)-C(16)-C(21)-C(20)	-178.95(16)
C(19)-C(20)-C(21)-C(16)	-0.3(3)
C(15)-N(1)-C(22)-C(23)	-12.7(7)
C(15)-N(1)-C(22)-C(27)	164.1(3)
N(1)-C(22)-C(23)-C(24)	176.7(8)
C(27)-C(22)-C(23)-C(24)	0.0
C(22)-C(23)-C(24)-C(25)	0.0

Table 17 (cont.)

C(23)-C(24)-C(25)-F(1)	-178.8(5)
C(23)-C(24)-C(25)-C(26)	0.0
F(1)-C(25)-C(26)-C(27)	178.7(5)
C(24)-C(25)-C(26)-C(27)	0.0
C(25)-C(26)-C(27)-C(22)	0.0
N(1)-C(22)-C(27)-C(26)	-176.9(7)
C(23)-C(22)-C(27)-C(26)	0.0
C(15)-N(1)-C(22A)-C(23A)	-19.8(7)
C(15)-N(1)-C(22A)-C(27A)	163.1(3)
C(27A)-C(22A)-C(23A)-C(24A)	0.0
N(1)-C(22A)-C(23A)-C(24A)	-177.1(9)
C(22A)-C(23A)-C(24A)-C(25A)	0.0
C(23A)-C(24A)-C(25A)-F(1A)	-178.9(6)
C(23A)-C(24A)-C(25A)-C(26A)	0.0
F(1A)-C(25A)-C(26A)-C(27A)	179.0(6)
C(24A)-C(25A)-C(26A)-C(27A)	0.0
C(25A)-C(26A)-C(27A)-C(22A)	0.0
C(23A)-C(22A)-C(27A)-C(26A)	0.0
N(1)-C(22A)-C(27A)-C(26A)	177.1(9)

Symmetry transformations used to generate equivalent atoms:

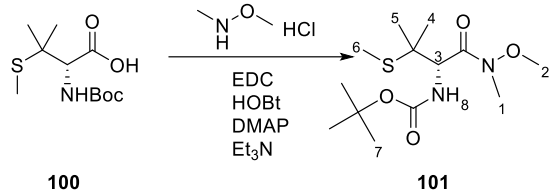
Table 18. Hydrogen bonds for dd75usa [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...S(1)	0.84(2)	2.80(2)	3.2043(15)	111.7(18)

Symmetry transformations used to generate equivalent atoms:

Experimental for Chapter 3

Preparation of *tert*-Butyl (*S*)-(1-(methoxy(methyl)amino)-3-methyl-3-(methylthio)-1-oxobutan-2-yl)carbamate (101)



100 **101**

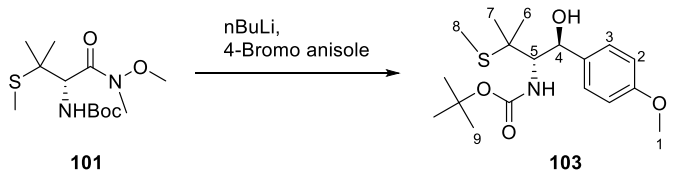
To a stirring solution of **100** (12 mmol, 1 equiv) in DMF (60 mL, 0.2M) cooled to 0 °C was added triethylamine (96 mmol, 8 equiv), DMAP (1.2 mmol, 0.1 equiv) and HOBt (12 mmol, 1 equiv). The reaction was stirred for 30 min and then in a single portion Weinreb Amine HCl (60 mmol, 5 equiv) was added. The reaction was stirred for an additional 12 h after which time TLC analysis indicated that the reaction was complete. The reaction was diluted with water (100 mL) and 10% Citric acid (80 mL) then extracted 3 x 50 ml EtOAc. The organics were pooled and washed 1 x 50 mL brine and dried over Na_2SO_4. The volatiles were removed under reduced pressure to yield an off white solid which was purified by column chromatography (30% EtOAc/Hex) to afford a white solid (8.8 mmol, 2.71 g, 74%).

Data for **101**:

^{1}H NMR: (400 MHz, $CDCl_3$)

5.40 (d; 1H; *J* = 10.2 Hz; CH (3)), 4.94 (d; 1H; *J* = 10.2 Hz; NH (8)), 3.79 (s; 3H; CH (2)), 3.21 (s; 3H; CH (1)), 2.08 (s; 3H; CH (6)), 1.42 (s; 9H; CH (7)), 1.32 (s; 6H; CH (4,5))

Preparation of *tert*-Butyl ((1*S*,2*S*)-1-hydroxy-1-(4-methoxyphenyl)-3-methyl-3-(methylthio)butan-2-yl)carbamate (103)



101 **103**

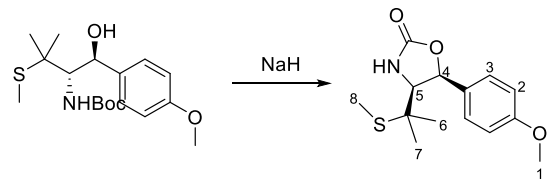
To a flame dried 100 ml schlenk flask was added 4-bromoanisole (55 mmol, 5 equiv) and dissolved in THF (55 ml, 1M). The flask was cooled to an internal temperature of -78 °C (dry ice/acetone) and subsequently *n*-BuLi (2.55M, 4.99 equiv) was added dropwise via syringe. The solution was maintained at an internal temperature of -78 °C for 1 h after which time the solution was cannulaed dropwise into a flame dried, 250 mLl round bottomed flask containing dissolved **101** (11 mmol, 1 equiv) in anhydrous THF (0.2M, 55 mL) at an internal temperature of -40 °C (dry ice/MeCN). After the addition, the reaction was stirred for an additional 30 min at which time it was rapidly poured into a vigorously stirred phosphate buffer (1M, pH 7, 100 mL). The aqueous solution containing the aryl ketone product **102** was poured into a 1L sepratory funnel containing EtOAc (50 mL). The aqueous layer was subsequently extracted 2 x 50 mL EtOAc. The organics were pooled, washed with brine (1 x 25 mL) and dried over sodium sulfate. The volatiles were removed and the resulting residue was taken up in anhydrous Methanol (100 mL) and cooled to an internal temperature of -20 °C (dry ice/sat. CaSO4) [Note: any exotherm above -20 °C results in eroded diastereoselectivity]. Then $NaBH_4$ (2 equiv, 22 mmol) was added portion-wise keeping the internal temperature at or below -20 °C. The reaction was maintained at -20 °C for 2 h after which time water (50 mL) was added to the reaction mixture and the mixture extracted with EtOAc (3 x 50 mL). The organics were pooled, washed with brine (1 x 25 mL) and dried over sodium sulfate. The volatiles were removed under reduced pressure and the resulting residue purified by column chromatography (50% EtOAc/Hexanes) to give **103** as an off white solid (5.9 mmol, 54%, d.r. >20:1)

Data for **103**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 (d; 2H; *J* = 8.6 Hz; CH (3)), 6.88 (d; 2H; *J* = 8.6 Hz; CH (2)), 4.85 (d; 1H; *J* = 7.4 Hz; CH (4)), 4.40 (d; 1H; *J* = 7.4 Hz; CH (5)), 3.81 (s; 3H; CH (1)), 2.22 (s; 3H; CH (8)), 1.42 (s; 3H; CH (6,7)), 1.31 (s; 3H; CH (6,7)), 1.28 (s; 9H; CH (9))

Preparation of (4*S*,5*S*)-5-(4-Methoxyphenyl)-4-(2-(methylthio)propan-2-yl)oxazolidin-2-one (104)



103 **104**

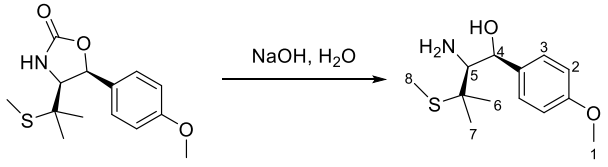
To a flame dried 100 mL Schlenk flask with stir bar was added **103** (1.8 mmol, 1 equiv) and dissolved in DMF (0.2M, 9 mL). The reaction was cooled to 0 °C in an ice bath and sodium hydride (3.6 mmol, 2 equiv) was added portion-wise over 5 min. The reaction was warmed to 25 °C over 12 h after which time water (5 mL) was added to the reaction flask and the reaction poured into a sepratory funnel. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The organics were pooled and dried over sodium sulfate and volatiles removed under reduced pressure to give an off white solid. The crude material was purified by column chromatography (20% EtOAc/Hex) to give **104** as a white solid (1.7 mmol, 495 mg, 98%)

Data for **104**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.34 (d; 2H; *J* = 8.3 Hz; CH (3)), 6.91 (d; 2H; *J* = 8.3 Hz; CH (2)), 5.75 (d; 1H; *J* = 7.5 Hz; CH (4)), 4.04 (d; 1H; *J* = 7.5 Hz; CH (5)), 3.83 (s; 3H; CH (1)), 2.01 (s; 3H; CH (6,7)), 1.06 (s; 3H; CH (6,7)), 0.90 (s; 3H; CH (8))

Preparation of (*1S*,2*S*)-2-Amino-1-(4-methoxyphenyl)-3-methyl-3-(methylthio)butan-1-ol (105)



104 **105**

To a 50 mL round bottomed flask equipped with reflux condenser was added 1M NaOH (5 equiv) in MeOH (0.2 M, 8.5 mL). Then **104** (1 equiv, 1.7 mmol) was added in a single portion and the reaction heated to reflux for 6 h. The reaction was quenched with 10 mL of 10% citric acid and poured into a seperatory funnel. The aqueous layer was extracted 3 x 30 ml CH_2Cl_2. The organics were pooled and dried with sodium sulfate and the volatiles were removed under

reduced pressure. The crude material was purified by column chromatography (3% MeOH/DCM) to afford **105** as a white solid (1.58 mmol, 404 mg, 85%)

Data for **105**:

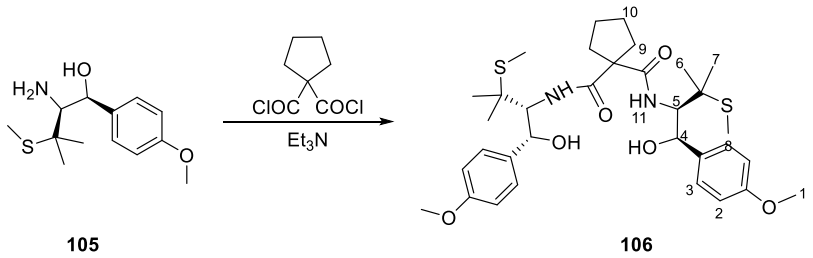
^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 (d; 2H; *J* = 8.6 Hz; CH (3)), 6.88 (d; 2H *J* = 8.6 Hz; CH (2)), 4.66 (d; 1H; *J* = 7.0 Hz; CH (4)), 3.80 (s; 3H; CH (1)), 3.05 (d; 1H; *J* = 7.0 Hz; CH (5)), 2.11 (s; 3H; CH (6,7)), 1.36 (s; 3H; CH (6,7)), 1.24 (s; 3H; CH (8))

^{13}C NMR: (126 MHz, $CDCl_3$)

159.5, 134.9, 128.8, 114.0, 75.4, 61.1, 55.5, 47.9, 25.7, 24.5, 11.1

Preparation of N,N'-Bis((1*R*,2*R*)-1-hydroxy-1-(4-methoxyphenyl)-3-methyl-3-(methylthio)butan-2-yl)cyclopentane-1,1-dicarboxamide (106)



105 106

To a flame dried 10 mL Schlenk flask was added **105** (2 equiv, 0.54 mmol) and dissolved in anhydrous CH_2Cl_2 (4 mL, 0.1M) and cooled to 0 °C. Then, via syringe, triethylamine (5 equiv, 1.35 mmol) was added to the reaction mixture followed by dropwise addition of cyclopentane-1,1-dicarbonyl dichloride (1 equiv, 0.27 mmol). The reaction was stirred for 3 h after which time water (5 mL) was added to the reaction. The biphasic mixture was poured into a seperatory funnel and diluted with CH_2Cl_2 (10 mL) and saturated sodium bicarbonate (10 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 10 mL) and the organics pooled, washed with brine (10 mL) and dried over sodium sulfate. The volatiles were removed under reduced pressure and the resulting off white residue was purified by column chromatography (EtOAc) to afford **106** as a white solid (0.19 mmol, 120 mg, 70%).

Data for **106**:

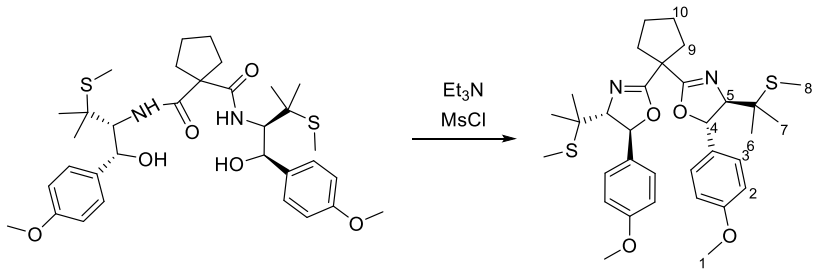
^{1}H NMR: (500 MHz, $CDCl_3$)

7.24 (d; 4H; *J* = 8.5 Hz; CH (3)), 6.81 (d; 4H; *J* = 8.5 Hz; CH (2)), 6.34 (d; 2H; *J* = 10.2 Hz; CH (4)), 4.83 (d; 2H; *J* = 7.3 Hz; NH (11)), 4.36 (dd; 2H; *J* = 10.2, 7.3 Hz; CH (5)), 3.75 (s; 6H; CH (1)), 2.15 (s; 6H; CH (6,7)), 1.31 (s; 6H; CH (6,7)), 1.28 – 1.01 (m; 14H; CH (9,10))

^{13}C NMR: (126 MHz, $CDCl_3$)

172.1, 159.5, 134.1, 128.7, 113.9, 75.3, 61.4, 59.3, 55.5, 47.2, 34.0, 27.4, 25.4, 24.3, 11.6

Preparation of (4*R*,4'*R*,5*S*,5'*S*)-2,2'-(Cyclopentane-1,1-diyl)bis(5-(4-methoxyphenyl)-4-(2-(methylthio)propan-2-yl)-4,5-dihydrooxazole) (98)



106 **98**

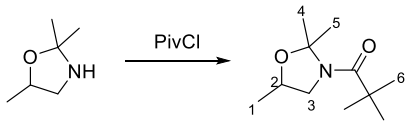
To a flame dried 50 mL Schlenk flask containing a solution of **106** (1 equiv, 0.16 mmol) in anhydrous CH_2Cl_2 (0.02M, 8 ml) was added triethylamine (10 equiv, 1.6 mmol) and then dropwise Mesyl Chloride (4 equiv, 0.64 mmol). The reaction was heated to 40 °C until the starting material was consumed. Water (5 mL) was added to the reaction mixture and the biphasic solution poured into a sepratory funnel. The organics were further diluted with an additional 5 mL of saturated sodium bicarbonate and extracted with CH_2Cl_2 (3 x 15 mL). The organics were pooled a dried with sodium sulfate and the volatiles removed under reduced pressure. The residue was purified by column chromatography (50% EtOAc:Hexanes) and subsequently recrystallized from Hexanes to afford **98** as white crystals (0.054 mmol, 33 mg, 34%).

Data for **98**:

^{1}H NMR: (400 MHz $CDCl_3$)

7.21 (d; 4H; *J* = 8.5 Hz; CH (3)), 6.66 (d; 4H; *J* = 8.5 Hz; CH (2)), 5.39 (d; 2H; *J* = 6.5 Hz; CH (4)), 4.03 (d; 2H; *J* = 6.5 Hz; CH (5)), 3.75 (s; 6H; CH (1)), 2.56 (dt; 2H; *J* = 13.2, 6.4 Hz; CH (9,10)), 2.23 (dt; 2H; *J* = 13.4, 6.1 Hz; CH (9,10)), 1.86 – 1.68 (m; 10 H; CH (8,9,10)), 1.40 (s; 6H; CH (6,7)), 1.14 (s; 6H; CH (6,7))

Preparation of 2,2-dimethyl-1-(2,2,5-trimethyloxazolidin-3-yl)propan-1-one (110)



110a **110**

To a flame dried 25 mL Schlenk flask containing 2,2,5-trimethyloxazolidine **110a** (2.17 mmol, 1 equiv) was added CH_2Cl_2 (0.2 M, 6 mL) and triethylamine (3 equiv, 2.54 mmol). The reaction mixture was cooled to 0 °C in an ice bath and pivolyl chloride (1.1 equiv, 2.38 mmol) was added dropwise. The reaction was allowed to warm to 25 °C and stirred for 4 h. The reaction was quenched by the dropwise addition of saturated sodium bicarbonate (5 mL) and decanted into a seperatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), the organics pooled and dried over sodium sulfate. The volatiles were removed under reduced pressure and the resulting residue purified by column chromatography (25% EtOAc/Hex) to afford a slightly yellow solid (1.6 mmol, 320 mg, 74%)

Data for **110**:

^{1}H NMR: (500 MHz, $CDCl_3$)

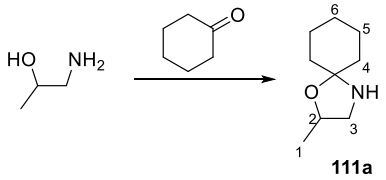
4.26 – 4.17 (m; 1H; CH (2)), 3.96 (dd; 1H; *J* = 9.3, 5.1 Hz; CH (3)), 3.19 (dd; 1H; *J* = 9.3 Hz; CH (3)), 1.65 (s; 3H; CH (1)), 1.60 (s; 3H; CH (4,5)), 1.37 (d; 3H; *J* = 5.1 Hz; CH (4,5)), 1.28 (s; 9H; CH (6))

^{13}C NMR: (126 MHz, $CDCl_3$)

174.4, 96.5, 70.4, 53.4, 39.6, 27.3, 26.2, 23.8, 17.8

TLC: R_f = 0.60 (EtOAc/Hexanes 1:4) [Iodine, CAM]

Preparation of 2-Methyl-1-oxa-4-azaspiro[4.5]decane (111a)



111a

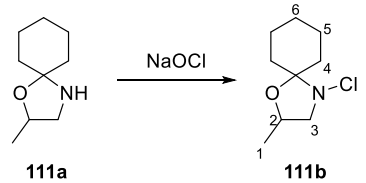
To a 250 mL round bottomed flask equipped with Teflon stirbar and reflux condenser was added benzene (0.25 M, 100 mL), 1-aminopropan-2-ol (1 equiv, 20 mmol) and cyclohexanone (5 equiv, 100 mmol). Then *p*-toluenesolfonic acid monohydrate (0.1 equiv, 2 mmol) was added in a single portion and the mixture heated to reflux for 18 h. After 18 h the benzene was removed under reduced pressure (30 mmHg) and the residue was fractionally distilled under reduced pressure (90-96 °C, 0.1 mmHg) to afford **111a** as a clear oil (14 mmol, 2.15g, 70%).

Data for **111a**:

^{1}H NMR (500 MHz, $CDCl_3$)

4.05 (m; 1H; CH (2)), 3.28 (ddd; 1H; *J* = 11.8, 6.2, 1.2 Hz; CH (3)), 2.71 (ddd; 1H; *J* = 11.9, 6.7, 1.3 Hz; CH (3)), 2.01 – 1.83 (m; 2H; CH (4)), 1.73 – 1.52 (m; 9H; CH(1, 5, 6)), 1.24 (d; 2H; *J* = 6.1 Hz; CH(5,6))

Preparation of 4-Chloro-2-methyl-1-oxa-4-azaspiro[4.5]decane (111b)



111a **111b**

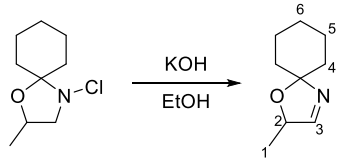
To a 1L round bottomed flask with Teflon stir bar was added commercial bleach (5.25% NaOCl, 5 equiv, 50 mmol) and cooled to 0 °C. Then **111a** was added dropwise to the stirring solution and the temperature maintained below 18 °C for 3 h. During this time the solution changes from yellow to light yellow/clear. The reaction is decanted into a seperatory funnel and extracted with CH_2Cl_2 (3 x 50 mL). The organics are pooled, dried over sodium sulfate, and the volatiles removed under reduced pressure to afford a light yellow oil that is used without further purification (8.4 mmol, 1.58g, 84%).

Data for **111b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

4.43 (m; 1H; CH (2)), 3.74 (dd; 1H; *J* = 13.6, 6.5 Hz; CH (3)), 3.35 (dd; 1H; *J* = 13.7, 7.8 Hz; CH(3)), 1.93 – 1.40 (m; 11H; CH (1,4,5,6)), 1.37 (d; 2H; *J* = 6.1 Hz; CH (6))

Preparation of 2-Methyl-1-oxa-4-azaspiro[4.5]dec-3-ene (111)



30 **12**

To a 10 ml round bottomed flask with Teflon stir bar containing a solution of KOH (1 equiv, 5.5 mmol) in ethanol (7M, 785 mL) cooled to 0 °C was added **111b** (1 equiv, 5.5 mmol) in ethanol (7M, 785 mL). The reaction was stirred at 0 °C for 1 h during which time it became dark brown. The reaction was diluted with water (20 mL) and poured into a seperatory funnel and extracted with CH_2Cl_2 (3 x 30 mL), the organics pooled and washed with brine and dried over sodium sulfate. The volatiles were removed under reduced pressure to give a yellow oil which was purified by column chromatography (grade III basic alumina, 10% CH_2Cl_2/Hexanes) to afford a clear oil (2.53 mmol, 380 mg, 46%).

Data for **111**:

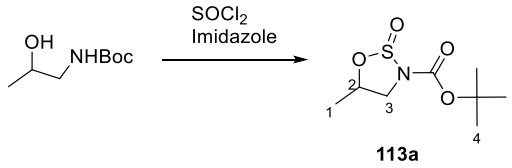
^{1}H NMR: (500 MHz, $CDCl_3$)

7.38 (s; 1H; CH (3)), 4.86 (q; 1H; *J* = 6.7 Hz; CH (2)), 1.83 – 1.46 (m; 10H; CH (4,5,6)), 1.36 (d; 3H; *J* = 6.7 Hz; CH (1))

HRMS: (ES+)

Found: 154.1227; Calc. for $C_9H_{15}NO$: 154.1154

Preparation of *tert*-Butyl 5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2-oxide (31)



113a

To a flame dried, two necked 250 mL round bottomed flask equipped with addition funnel topped with argon inlet and septa containing imidazole (4 equiv, 34 mmol) was added CH_2Cl_2 (40 mL) followed by triethylamine (2 equiv, 17 mmol). The reaction was stirred for 5 min after which time thionyl chloride (1.1 equiv, 9.35 mmol) was added dropwise at room temperature. The reaction was stirred for 15 min and then cooled to -60 °C (dry ice/$CHCl_3$). Then a solution of *tert*-butyl (2-hydroxypropyl)carbamate (1 equiv, 8.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise. The reaction was stirred for 3 h maintaining an internal temperature of -60 °C. After completion, the reaction was quenched by the addition of water (50 mL), the phases separated, the organic phase was washed with brine (50 mL) and dried over sodium sulfate. The volatiles were removed and the resulting white solid (mixture of diastereomers, d.r. = 2.5:1) was pure enough to carry forward to the next reaction (7.82 mmol, 1.75g, 92%). A small portion was purified by silica gel chromatography for analytical purposes (15% EtOAc/Hex).

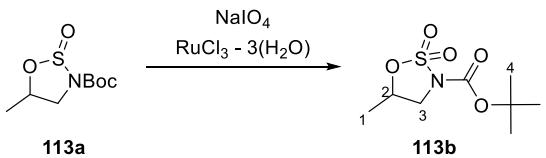
Data for **113a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

5.42 (dt; 1H; *J* = 11.5, 6.1 Hz; CH (2)), 3.93 (dd; 1H; *J* = 9.2, 5.7 Hz; CH (3)), 3.16 (t; 1H; *J* = 10.1 Hz; CH (3)), 1.56 (d; 3H; *J* = 6.1 Hz; CH (1)), 1.54 (s; 9H; CH (4)). (major diastereomer)

TLC: R_f = 0.52 (EtOAc/Hexanes 1:4) [Iodine, CAM]

Preparation of *tert*-Butyl 5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (113b)



113a **113b**

To a 500 mL round bottomed flask with a Teflon stir bar was added **113a** (1 equiv, 7.8 mmol) and dissolved in MeCN (50 mL) and cooled to 0 °C in an ice water bath. Then $NaIO_4$ (1.1

equiv, 8.58 mmol), $RuCl_3 \bullet 3H_2O$ (0.01 equiv, 0.07 mmol) and water (50 mL) were sequentially added to the reaction mixture. The reaction was stirred for 3 h until complete as indicated by TLC. The cold reaction was diluted with water (50 mL) and extracted with Et_2O (3 x 100 ml), washed with brine, and dried over sodium sulfate. The volatiles were removed under reduced pressure to give a white solid which was purified by silica gel chromatography (25% EtOAc/Hexanes) to give a white solid (6.4 mmol, 1.66 g. 81%)

Data for **113b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

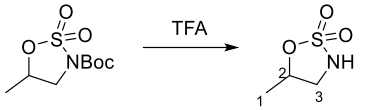
5.01 (dp; 1H; *J* = 9.4, 6.1 Hz, CH (2)), 4.12 (dd; 1H; *J* = 10.0, 5.6 Hz; CH (3)), 3.69 (t; 1H; *J* = 9.7 Hz; CH(3)), 1.63 (d; 3H; *J* = 6.7 Hz; CH (1)), 1.59 (s; 9H; CH (4))

^{13}C NMR: (126 MHz, CDCl3)

148.6, 85.3, 76.2, 51.6, 27.8, 21.0

TLC: R_f = 0.44 (EtOAc/Hexanes 1:4) [Iodine, CAM]

Preparation of 5-Methyl-1,2,3-oxathiazolidine 2,2-dioxide (113c)



113b **113c**

To a flame dried 100 mL Schlenk flask was added **113b** (1 equiv, 7 mmol) and dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °C. Then via syringe trifluoroacetic acid (5 equiv, 35 mmol) was added to the reaction and the reaction warmed to room temperature and stirred at room temperature for 18 h. The reaction was quenched with saturated sodium carbonate and the organics decanted from the aqueous, dried over sodium sulfate and the volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography (20% MeOH/ CH_2Cl_2) to afford **113c** as a light brown oil (3.36 mmol, 410 mg, 48%).

Data for **113c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

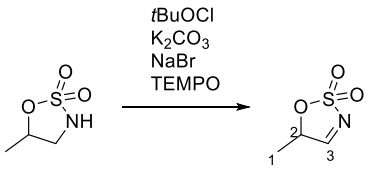
4.98 (dp; 1H; *J* = 7.8, 6.1 Hz; CH (2)), 3.77 (dd; 1H; *J* = 11.8, 5.9 Hz; CH (3)), 3.41 – 3.30 (m; 1H; CH (3)), 1.56 (d; 3H; *J* = 6.1 Hz; CH (1)).

^{13}C NMR: (126 MHz, $CDCl_3$)

81.8, 50.1, 18.9

TLC: R_f = 0.36 (EtOAc/Hexanes 1:1) [Iodine, CAM]

Preparation of 5-Methyl-5H-1,2,3-oxathiazole 2,2-dioxide (113)



113c **113**

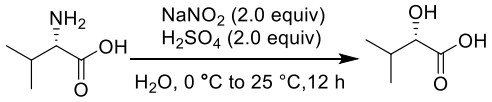
To a solution of **113c** (1 equiv, 0.36 mmol), KBr (1 equiv, 0.36 mmol), and sodium sulfate (2 equiv, 0.72 mmol) in MeCN (3 mL) was added *t*-BuOCl (1.1 equiv, 0.39 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 1 h. Then, TEMPO (0.1 equiv, 0.04 mmol) was added to the mixture solution at room temperature and stirred at room temperature for 30 min. To the solution was added sodium carbonate (1 equiv, 0.36 mmol) at room temperature, and the obtained mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with water (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL), dried over sodium sulfate and the volatiles removed under reduced pressure to afford an yellow oil which was used without further purification (0.18 mmol, 25 mg, 50%).

Data for **113**:

^{1}H NMR: (500 MHz, $CDCl_3$)

8.4 (s; 1H; CH (3)), 5.45 (q; 1H; *J* = 7.1 Hz; CH (2)), 1.72 (d; 3H; *J* = 7.1 Hz; CH (1))

Preparation of (*S*)-2-Hydroxy-3-Methylbutanoic acid (123)



S27

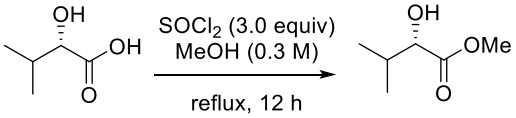
L-Valine (8.78 g, 75.0 mmol) was placed into a 300 mL, three-necked flask containing an egg-shaped stir bar (50.8 × 19.1 mm), and water (75 mL) was added. The flask was fitted with two addition funnels. In one addition funnel concentrated H_2SO_4 (14.71 g, 8.0 mL, 150.0 mmol, 2.0 equiv) was added. To the other addition funnel a solution of $NaNO_2$ (10.35 g, 150 mmol, 2.0 equiv) dissolved in H_2O (25 mL) was added. The reaction vessel was cooled to 0 °C using ice bath, and the acid was added dropwise with stirring for 2 min. After the L-valine dissolved, the sodium nitrite solution was added dropwise by syringe, and the rate of addition of the acid was adjusted similarly so as to maintain the internal temperature below 0 ^{o}C. After the addition was complete, the mixture was stirred at 0 °C for 1 h and then was stirred at 25 ^{o}C for 12 h. After this time, the reaction mixture was transferred to 500-mL separatory funnel and was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (300 mL) to afford **123** (5.80 g, 65%) as a white crystalline solid.

Data for **123:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.11 (d, *J* = 3.6 Hz, 1H), 2.11 (dtd, *J* = 13.7, 6.8, 3.5 Hz, 1H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H).

Preparation of Methyl (*S*)-2-Hydroxy-3-methylbutanoate (124a)



123 **124a**

A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **123** (5.80 g, 49.1 mmol) and MeOH (distilled, 120 mL) under nitrogen. The solution was cooled in an ice bath for 10 min and $SOCl_2$ (17.52 g, 10.74 mL, 147.3 mmol, 3.0 equiv) was added dropwise by syringe over 5 min at 0 ^{o}C. The mixture was heated to reflux

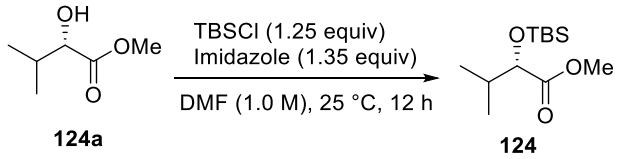
using a condenser in a 75 ^{o}C oil bath for 12 h. After the solution was cooled to 25 ^{o}C, the volatile components are removed by rotary evaporation (30 ^{o}C, 50 mbar). The resulting residue was diluted with ethyl acetate (200 mL) and sat. aq. $NaHCO_3$ (200 mL) was added slowly because of evolution of gas. The mixture was transferred to a 500-mL separatory funnel and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the organic layers were combined, washed brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (300 mL) to afford (4.40 g, 68%) **124a** as a colorless oil.

Data for **124a:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.02 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.76 (s, 3H), 2.78 (d, *J* = 6.1 Hz, 1H), 2.04 (ddp, *J* = 10.5, 6.9, 3.6 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 4H), 0.83 (d, *J* = 6.9 Hz, 4H).

Preparation of Methyl (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutanoate (124)



124a **124**

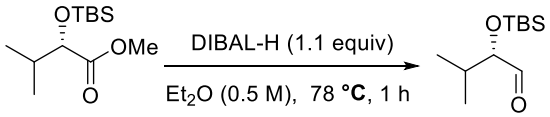
A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **124a** (4.40 g, 33.3 mmol), TBSCl (6.27 g, 41.6 mmol, 1.25 equiv), imidazole (3.06 g, 44.95 mmol, 1.35 equiv), and DMF (SDS, 45 mL) under nitrogen. The mixture was stirred at 25 ^{o}C for 12 h. The resulting mixture was diluted in Et_2O (200 mL) transferred to 500-mL separatory funnel and was washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **124** (7.50 g, 92%) as a colorless oil. The spectroscopic data for **S29** matched the literature values.

Data for **124:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.86 (d, *J* = 4.7 Hz, 1H), 3.58 (s, 3H), 1.99 – 1.86 (m, 1H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.81 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H), -0.06 (s, 3H), -0.07 (s, 3H).

Preparation of (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutanal (125a)



124 **125a**

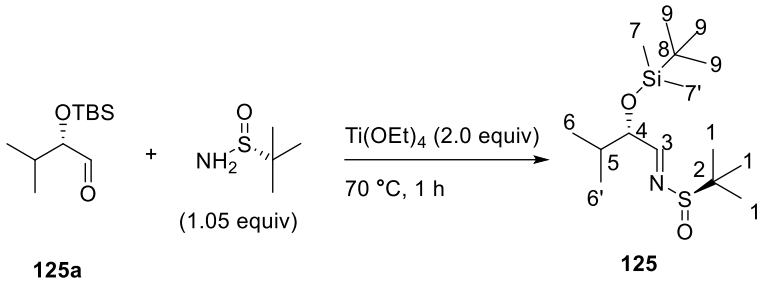
A 250-mL, 3-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe and two rubber septa was charged with **124** (7.60 g, 31.0 mmol) and Et_2O (60 mL, SDS) under nitrogen. The solution was cooled to -78 ^oC using cryocooler in an *i*-PrOH and DIBAL-H (1.0 M in heptane, 34.1 mL, 34.1 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below -70 ^oC. The solution was stirred at -78 ^oC for 1 h and then reaction was quenched with H_2O (6 mL). The mixture was slowly warmed to 25 ^oC. The mixture was stirred for additional 1 h. Then, the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with Et_2O (2 × 75 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^oC, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et_2O, 7:3 to afford **125a** (5.40 g, 80%) as a colorless oil.

Data for **125a:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 9.58 (s, 1H), 3.71 (dd, *J* = 4.9, 2.2 Hz, 1H), 2.07 – 1.96 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 4H), 0.91 (d, *J* = 7.4 Hz, 12H), 0.05 (s, 6H).

Preparation of (*R*)-*N*-((*S*,*E*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutylidene)-2-methylpropane-2-sulfinamide (125)



A 100-mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **125a** (4.98 g, 23.05 mmol), (*R*)-2-methylpropane-2-sulfinamide (2.93 g, 24.20 mmol, 1.05 equiv) and titanium (IV) ethoxide (10.51 g, 9.66 mL, 46.1 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 ^{o}C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200-mL Erlenmeyer flask with a stir bar and brine (5 mL), and the vial was rinsed with ethyl acetate (2 × 25 mL) to help the transfer. The suspension was stirred at 25 ^{o}C for 10 min and then, filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2 × 100 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **125** (6.93 g, 94%) as a yellow oil.

Data for **125:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.88 (d, *J* = 5.3 Hz, 1H, HC(7)), 4.12 (t, *J* = 5.1 Hz, 1H, HC(7)), 1.93 – 1.79 (m, 1H, HC(7)), 1.15 (s, 9H, HC(7)), 0.89 (dd, *J* = 6.9, 2.5 Hz, 6H, HC(7)), 0.84 (s, 9H, HC(7)), 0.01 (s, 3H, HC(7)), -0.04 (s, 3H, HC(7)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 171.6 (C(17)), 78.8 (C(17)), 56.7 (C(17)), 33.8 (C(17)), 25.8 (C(17)), 22.5 (C(17)), 18.8 (C(17)), 18.1 (C(17)), 17.9 (C(17)), -4.2 (C(17)), -4.9 (C(17)).

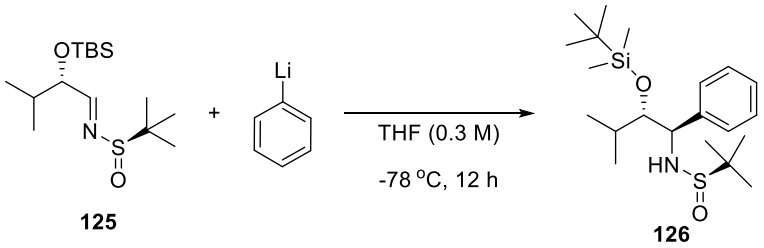
IR: (neat)

2958 (m), 2930 (m), 2859 (w), 1622 (w), 1472 (m), 1388 (w), 1363 (m), 1253 (m), 1139 (w), 1090 (s), 1006 (w), 938 (w), 860 (m), 837 (s), 776 (s), 683 (w), 665 (w), 584 (w), 501 (w).

HRMS: Calcd for $C_{15}H_{34}NO_2SSi$ $(MH)^+$: 320.2076, found: 320.2080

TLC: R_f 0.50 (silica gel, hexanes/EtOAc, 9:1, UV, $KMnO_4$)

Preparation of (*R*)-*N*-((2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-1-(4-(trifluoromethyl)phenyl)butyl)-2-methylpropane-2-sulfinamide (126)



A oven dried, 1 dram vial with an egg-shaped stir bar THF (1 mL) and **125** under nitrogen. The solution was cooled to -78 °C in an *i*-PrOH bath. Then, another 1 dram vial containing an egg-shaped stir bar was charged with TMEDA (60 mg, 0.50 mmol), phenyllithium (0.28 mL, 1.8M in ether) and THF (1 mL) under nitrogen. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at -78 °C using cryocooler in *i*-PrOH for 12 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (50 mL) at -78 °C, and then was slowly warmed to 25 °C. The mixture was transferred to a 60-mL separatory funnel. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the organic layers were combined, washed with brine (1 × 10 mL), dried over Na_2SO_4 (5 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 91:9 by ^1H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **126** (79 mg, 80%) as a yellow solid.

Data for **126:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.36 (d, *J* = 4.3 Hz, 4H), 7.31 (q, *J* = 4.0 Hz, 1H), 4.70 (dd, *J* = 4.9, 1.3 Hz, 1H), 4.17 (s, 1H), 3.83 (dd, *J* = 5.0, 2.4 Hz, 1H), 1.69 – 1.58 (m, 1H), 1.30 (s, 9H), 1.01 (s, 9H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.25 (s, 3H), 0.16 (s, 3H).

Experimental for Appendix A

Literature Preparations

The following compounds were prepared by literature methods and characterization data matched those previously reported: **147**[134], **148**[134], **149**[134], **150**[135], **151**[135], **152**[135], **159**[136], **160**[136], **161**[136], **162**[136].

Preparation of *tert*-Butyl(3-((2S,3S)-3-cinnamyloxiran-2-yl)propoxy)dimethylsilane (153)

152 **153**

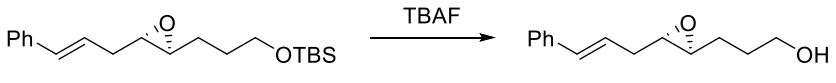
To an oven-dried, 100-mL, Schlenk flask fitted with a Teflon coated stirbar, internal digital thermometer and rubber septum under an Argon atmosphere was charged Copper(I) bromide dimethyl sulfide complex (119 mg, 0.58 mmol, 0.4 equiv) and anhydrous THF (12 mL). Iodide **152** (517 mg, 1.45 mmol) was charged in a single portion via syringe. Anhydrous HMPA (1.0 mL) was added and the suspension was immediately cooled to an internal temperature of -25 °C. (*E*)-styrylmagnesium bromide (722 mg, 3.48 mmol, 2.4 equiv) was added dropwise maintaining the internal temperature below -20 °C. After 2 h the reaction was judged complete by TLC analysis. The reaction mixture was quenched with addition of a saturated ammonium chloride solution (8 mL). The biphase was decanted into a 250 mL separatory funnel and further diluted with saturated ammonium chloride (8 mL). The solution was extracted with EtOAc (3 x 40 mL), the organics pooled and washed with saturated ammonium chloride (20 mL). The organics were dried over sodium sulfate (15 g) and the volitiles removed under reduced pressure (30 mmHg, 30 °C) to afford a light yellow oil. Purification by silica gel chromatography (1" x 6" silica gel, 20 mL fractions, gradient Hexanes (80 mL), Hex/EtOAc 24:1 (200 mL), Hex/EtOAc 9:1 (100 mL) to afford **153** as a clear oil (255 mg, 0.76 mmol, 53%).

Data for **153:**

^{1}H NMR: (500 MHz, $CDCl_3$)

7.45 – 7.22 (m, 5H), 6.54 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.33 – 6.18 (m, 1H), 3.79 – 3.59 (m, 2H), 2.92 – 2.83 (m, 1H), 2.52 (tdd, *J* = 6.7, 4.7, 1.4 Hz, 1H), 1.79 – 1.56 (m, 6H), 0.94 (s, 9H), 0.09 (s, 3H).

Preparation of 3-((2S,3S)-3-Cinnamyloxiran-2-yl)propan-1-ol (154)



153 **154**

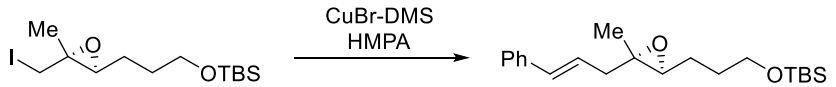
To an oven-dried, 50-mL, Schlenk flask equipped with rubber septum, digital thermometer under an atmosphere of argon added tetrabutylammonium fluoride (120 mg, 0.44 mmol, 2 equiv) and dissolved in THF (2.5 mL). The solution was cooled to an internal temperature of 2 °C in an ice/water bath. Compound **153** (97 mg, 0.29 mmol) was dissolved in THF (2.5 mL) and added dropwise to the solution. The reaction mixture was slowly warmed to 25 °C over 2 h. The reaction was judged complete by TLC analysis (9:1 Hex/EtOAc) after 12 h. Water (5 mL) was added to the reaction mixture and the solution was decanted into a 60 mL separatory funnel. An additional 30 mL of water was added and the biphase was extracted with EtOAc (3 x 15 mL). The organics were pooled and dried over sodium sulfate (10 g). The volitiles were removed under reduced pressure (30 mmHg, 30 °C) to afford a light yellow oil. The crude material was purified by silica gel chromatography (1" x 6" silica, 10 mL fractions, 1:1 Hex/EtOAc) to afford the desired compound **154** as a clear oil. (57 mg, 0.29 mmol, 90%)

Data for **154:**

^{1}H NMR: (500 MHz, $CDCl_3$)

7.42 – 7.29 (m, 5H), 6.55 – 6.45 (m, 1H), 6.23 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.72 (td, *J* = 6.3, 2.1 Hz, 2H), 2.91 (td, *J* = 5.4, 2.2 Hz, 1H), 2.85 (ddd, *J* = 6.7, 4.2, 2.3 Hz, 1H), 2.53 – 2.44 (m, 2H), 1.88 – 1.80 (m, 1H), 1.80 – 1.67 (m, 3H), 1.58 (dt, *J* = 13.7, 7.1 Hz, 1H).

Preparation of *tert*-Butyl(3-((2S,3S)-3-cinnamyl-3-methyloxiran-2-yl)propoxy)dimethylsilane (164)



163 **164**

To an oven-dried, 100-mL, Schlenk flask fitted with a Teflon coated stirbar, internal digital thermometer and rubber septum under an Argon atmosphere was charged Copper(I) bromide dimethyl sulfide complex (248 mg, 1.30 mmol, 0.5 equiv) and anhydrous THF (12 mL).

Iodide **164** (1.29g, 2.61 mmol) was charged in a single portion via syringe. Anhydrous HMPA (1.8 mL) was added and the suspension was immediately cooled to an internal temperature of -25 °C. (*E*)-styrylmagnesium bromide (1.08g, 5.22 mmol, 2 equiv) was added dropwise maintaining the internal temperature below -20 °C. After 2 h the reaction was judged complete by TLC analysis. The reaction mixture was quenched with addition of a saturated ammonium chloride solution (8 mL). The biphase was decanted into a 250 mL separatory funnel and further diluted with saturated ammonium chloride (8 mL). The solution was extracted with EtOAc (3 x 40 mL), the organics pooled and washed with saturated ammonium chloride (20 mL). The organics were dried over sodium sulfate (15 g) and the volitiles removed under reduced pressure (30 mmHg, 30 °C) to afford a light yellow oil. Purification by silica gel chromatography (1" x 6" silica gel, 20 mL fractions, gradient Hexanes (80 mL), Hex/EtOAc 24:1 (200 mL), Hex/EtOAc 9:1 (100 mL) to afford **164** as a clear oil (510 mg, 2.61 mmol, 41%).

Data for **164:**

^{1}H NMR: (500 MHz, $CDCl_3$)

7.73 (m, 5H), 7.58 – 7.16 (m, 10H), 6.51 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.24 (dt, *J* = 15.7, 7.3 Hz, 1H), 3.78 (ddt, *J* = 8.7, 5.6, 2.5 Hz, 2H), 3.27 (d, *J* = 9.8 Hz, 1H), 3.12 (d, *J* = 9.8 Hz, 1H), 2.88 (t, *J* = 5.9 Hz, 1H), 2.54 (ddd, *J* = 14.4, 7.5, 1.3 Hz, 1H), 2.44 (ddd, *J* = 14.4, 7.1, 1.5 Hz, 1H), 1.91 – 1.68 (m, 2H), 1.35 (s, 3H), 1.12 (d, *J* = 3.2 Hz, 9H).

Preparation of 3-((2*S*,3*S*)-3-Cinnamyl-3-methyloxiran-2-yl)propan-1-ol (157)

164 **157**

To an oven-dried, 50-mL, Schlenk flask equipped with rubber septum, digital thermometer under an atmosphere of argon added tetrabutylammonium fluoride (708 mg, 2.71 mmol, 2 equiv) and dissolved in THF (10 mL). The solution was cooled to an internal temperature of 2 °C in an ice/water bath. Compound **153** (510 mg, 1.08 mmol) was dissolved in THF (10 mL) and added dropwise to the solution. The reaction mixture was slowly warmed to 25 °C over 2 h. The reaction was judged complete by TLC analysis (9:1 Hex/EtOAc) after 12 h. Water (5 mL) was added to the reaction mixture and the solution was decanted into a 60 mL separatory funnel. An

additional 30 mL of water was added and the biphase was extracted with EtOAc (3 x 15 mL). The organics were pooled and dried over sodium sulfate (10 g). The volitiles were removed under reduced pressure (30 mmHg, 30 °C) to afford a light yellow oil. The crude material was purified by silica gel chromatography (1" x 6" silica, 10 mL fractions, 1:1 Hex/EtOAc) to afford the desired compound **154** as a clear oil. (193 mg, 0.83 mmol, 77%)

Data for **157:**

^{1}H NMR: (500 MHz, $CDCl_3$)

7.47 – 7.18 (m, 5H), 6.49 (dt, J = 15.7, 1.4 Hz, 1H), 6.21 (dt, J = 15.8, 7.3 Hz, 1H), 3.78 – 3.62 (m, 3H), 3.27 (d, J = 9.8 Hz, 1H), 3.13 (d, J = 9.9 Hz, 1H), 2.95 (dd, J = 7.0, 5.1 Hz, 1H), 2.93 – 2.84 (m, 1H), 2.53 (ddd, J = 14.4, 7.5, 1.3 Hz, 1H), 2.43 (ddd, J = 14.3, 7.1, 1.5 Hz, 1H), 1.35 (s, 3H).

Experimental for Appendix B

Literature Preparations

The following compounds were prepared by literature methods and characterization data matched those previously reported: **168**[137], **170**[138].